SECOND SERIES FEBRUARY 1942 VOL. 18, NO. 2

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

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Published monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York

Entered as second-class matter, February 3, 1928, at the Post Office at New York, N. Y., under the Act of August 24, 1912. Subscription, United States, Canada and Cuba, $3.00; all other countries, $4.00 a year. Single copies, 50c.

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

FEBRUARY 1942

INFLUENCE OF EXTRINSIC FACTORS ON THE CORONARY FLOW AND CLINICAL COURSE OF HEART DISEASE*

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THERE are a great many clinical observations associated with heart disease, and especially with angina pectoris, which are difficult to explain only on the basis of intrinsic anatomical changes in the coronary vessels alone, and can best be explained by the assumption of vasomotor changes in the caliber of the coronary vessels, decreasing the flow volume. Such an assumption of vasomotor changes is not new, and has been made by a great many men at many times. I would like here to review some of the experimental and clinical evidence indicating that such a decrease in flow may occur in response to autonomic stimuli of various origins, and that such decreases in coronary flow from extrinsic factors may produce the same disproportion between blood supply and blood needs, as do intrinsic anatomical changes in the vessel walls, which restrict the coronary flow when additional demands are made upon it.

I am not unmindful of the importance of the intrinsic factors. The point which I wish to make is this, that both intrinsic and extrinsic factors are valent in the restriction of coronary flow in proportions which

* Presented October 22, 1941 at the Graduate Fortnight of The New York Academy of Medicine.

vary in different cases. But the intrinsic factors are not reversible, and the conditions imposed are permanent, and must be compensated for in various ways by various means. The extrinsic factors are reversible and their influence may be lessened or may be obviated altogether.

It is not necessary to enter into a discussion of the nervous control of the coronary vessels. I think that it may be assumed as rather generally accepted that the vagus nerve exerts a tonic vasoconstrictor effect upon the coronary vessels, varying in degree with different physiological conditions, and that vasoconstrictor impulses are carried by the vagus. In like manner, it may be assumed that vasodilator impulses are carried through the sympathetic fibers, and that there is also some degree of vasodilator tone present in the vessels.

Anrep,[1] in 1926, described a reflex vasoconstriction of the coronary arteries consequent upon increased intracephalic pressure. The pathway for this vasoconstrictor impulse was through the vagus. Stella[2] and others confirmed this, and showed that this was mediated through the carotid sinus.

Clinically, attacks of angina pectoris or of paroxysmal dyspnea are seen to occur occasionally when the blood pressure reaches a point higher than that usual for the individual. That the attacks are not always due to an increase of the heart's work with the increased pressure, would seem to be indicated in the cases reported by Lewis,[3] in which the pain came on at a certain high level of blood pressure, and was relieved by the coronary vasodilator action of nitroglycerin, even though there was no fall in pressure.

The increased tendency to anginal pain following meals is a frequent clinical phenomenon. The symptoms may be explained in part by the increased work demanded of the heart during the earlier periods of digestion. This does not explain, however, why the pain is so frequently relieved by belching gas, or why it occurs at one time and not at another in the same person, under the same conditions. Anginal pain is very frequent also in hiatus hernia. The pain is more apt to occur when the herniation is present and is less apt to occur when the hernia is reduced.

That the anginal pain in these cases is due to a reflex vasoconstriction of the coronary arteries, is shown by the work of Dietrich and Schweigl in 1931, working with von Bergmann.[4] Distention of the stomach in the dog caused a marked decrease in the coronary flow, and this was espe-

cially so if the distention was at the esophageal hiatus. This decrease in flow did not occur after atropine, or if the vagi were sectioned. Fenn, LeRoy and I[5] repeated this work, with similar results. We further confirmed these results in the unanesthetized dog by distention of the stomach before and after atropine after a Rein stromuhr had been previously placed upon a branch of the coronary artery. Also, if the free abdominal cavity were distended with air, we again obtained a decrease in coronary flow, but not after vagotomy or atropine.

We obtained clinical confirmation of these experiments, using the method of Levy,[6] in which anginous patients are asked to breathe a low oxygen mixture until the first symptoms of anginal pain appear, when the patient is switched to straight oxygen and the attack ceases at once. If the patient breathed this low oxygen mixture after a meal, the pain came on sooner than it did in the control experiments done upon an empty stomach. If atropine was administered before the meal, the pain on a full stomach came on no sooner than it had originally in the control experiments. However, there were two groups of these patients in whom the time appearance of the pain was deferred by atropine. In some of them, the pain after a meal and after atropine came on at the same time as it had in the control experiments. In some others it took a longer time for the pain to occur after atropine than in the control, even though the experiment was done upon a full stomach. This would seem to indicate that in this second group, in which the pain did not occur as soon as in the control, the pain was due not only to intrinsic changes in the vessel walls, but to an extrinsic increase in vagal tone which had been released by the atropine. We then did another series of experiments upon the same patients, with an empty stomach, exactly as in the control experiments, but here we administered atropine before the experiment. In these experiments, the patients fell into the same two groups. One group experienced pain after the same time interval as in the control experiments, without the atropine. This group was the one in which there was more clinical reason to assume intrinsic changes in the vessel walls. The other group did not experience any symptoms for a longer time than had been noted in the control experiments, and a still longer time than that noted in the experiments done after a full meal. This group was that in which there was more clinical reason to assume the presence of an increased vagal tone, in addition to intrinsic vascular changes.

There is no need to emphasize the clinical importance of these observations in view of the frequency of anginal pain after meals. Master[7] has also shown the greater incidence of coronary thrombosis after meals.

In the experiments upon dogs, it was noted that the decrease in coronary flow was more marked if the distention was at the cardiac end of the stomach, and especially if the distending bag were against or in the esophageal hiatus. While hiatus hernia is being diagnosed more frequently than before, there is reason to think that it is still underdiagnosed, and its importance not fully realized. In a series of one hundred and seven cases of anginal pain followed in the last two years, in forty-four patients examined roentgenologically, there were eighteen or 17 per cent who showed a hiatus hernia. Just what the figure would be for a control series, I do not know, as I know of no control series to which some objection could not be made. But I do know that in the series of patients with angina pectoris and hiatus hernia, under our observation, there was a very clear history indicating the influence of the herniation upon the occurrence of the anginal pain, and that medical management of the hernia was apparently a factor in relief of these patients. It is to be emphasized that the anginal pain in hiatus hernia is not merely "anginalike," but that it is a real anginal pain resulting from an insufficient blood supply to the heart muscle.

Dr. Van Dellen has a case of hiatus hernia under observation at present, in which the electrocardiogram is normal when the herniation is not present, but in which there is a typical coronary curve present when the hernia occurs.

Hiatus hernia may also induce attacks of paroxysmal auricular fibrillation. I have seen two such cases in the last two months, in which there was very clear evidence that the attacks came on with the incidence of the hernia, and disappeared when the stomach slipped back into place. There is every reason to think that this occurrence is mediated through the vagus.

von Bergmann showed also that coronary vasoconstriction resulted from stimuli having their origin in the esophagus. We have all of us seen patients in whom attacks of angina were precipitated by the act of swallowing. Anginal pain is also found associated with diverticula of the esophagus and diverticula at the cardiac end of the stomach. Weiss and Ferris[8] reported a case in which Stokes-Adams attacks were brought

on by the act of swallowing. They showed that it was a vago-vagal reflex, and that it was clinically relieved by atropine.

Attacks of angina pectoris associated with gall bladder disease have been reported by several authors. Schwartz and Herman[9] reported that in most cases of gall bladder disturbance associated with cardiac symptoms, the heart symptoms were less after the operation. Fitz-Hugh and Wolferth[10] also showed an amelioration of the cardiac symptoms after gall bladder surgery, and showed that electrocardiographic changes tended to return to normal.

Some experiments which Fenn, LeRoy and I did upon the anesthetized dog could be interpreted as showing that there was a decrease in coronary flow upon distention of the gall bladder, but we did not consider our results wholly conclusive. In the last few weeks, Sheridan and I have repeated these experiments upon the decerebrate dog, and have obtained definite evidence of a decrease in coronary flow upon distention of the gall bladder, or distention or irritation of its ducts. This reflex did not occur after vagotomy, or after atropine.

It is possible, also that stimuli resulting from other abdominal conditions may initiate vasoconstrictor effects upon the coronary arteries. Angina pectoris is frequently associated with duodenal ulcer, a spastic duodenal bulb, a spastic colon, or diverticulosis of the colon. One can not be certain, however, how much the anginal symptoms are a result of reflexes arising from the abdominal conditions, and to what extent the anginal pain results from a common tendency to respond more readily than normal to vagal influence, or to the same lack in both cases of some inhibitions of this reflex, from higher centers. Experimentally, Smith and Miller[11] have shown that vagal reflexes may originate in the colon, as well as in the gall bladder. The part played by the gastrointestinal tract in producing cardiac symptoms has recently been reviewed by Morrison and Swalm.[12]

Danielopolu[13] long ago considered that stimuli arising from intrathoracic conditions might institute reflexes which decreased coronary flow, and such a thesis was in part the basis for operative interference to interrupt that reflex.

Scherf and Schönbrunner,[14] in 1937, published observations showing that lung emboli were associated with anginal pain, and similar observations have been reported since. DeTakats, Beck and Fenn[15] presented evidence indicating that there was a coronary vasoconstriction asso-

ciated with the lodging of an embolus in the pulmonary vessels, and that this was a reflex mediated through the vagus. The cases of heart block associated with pulmonary emboli reported by Kauffmann[16] would indicate vagal stimulation by the embolus. DeTakats and his co-workers have also shown a constriction of the pulmonary vessels, and of the bronchi, associated with pulmonary embolism.

DeTakats and Jesser[17] consider that such coronary vasoconstriction is the cause of death in many cases of pulmonary embolism, and that death is not always due to asphyxiation or right heart failure or incomplete venous return to the heart. Acting upon this hypothesis, and treating cases with atropine and papaverine, or atropine and aminophylline intravenously, resulted in a decrease in the death rate in their cases of pulmonary embolism from 82 per cent to 13 per cent.

Even more important from a clinical standpoint, is the work of Manning, McEachern and Hall,[18] showing that when a coronary artery of the dog is ligated, there is a reflex vasoconstriction of the other coronary vessels. When a coronary artery of the dog was ligated under full anesthesia, there was a very low mortality. But if the ligature were placed about the vessels under full anesthesia and not tied until several hours later, after recovery from the anesthetic, there was a very high mortality. But if the vagi were cut or atropine administered before the artery was ligated in the unanesthetized dog, the mortality remained at the same low level as when the artery was tied in a dog in which the reflexes were abolished by full anesthesia. In some work that has not as yet been published, LeRoy, Gilbert and Fenn have shown that when the artery is ligated, the mortality is not only less with atropine, but even less if a purine-base vasodilator is used.

These observations of Manning, McEachern and Hall are of very great clinical importance in the management of coronary thrombosis. Making use of these observations, we have very greatly reduced our mortality in early cases of coronary thrombosis, by the immediate administration of atropine and aminophylline. In addition, it must follow that if this secondary vasoconstriction was obviated, the infarct would be smaller and the myocardial damage less, with a better recovery and less loss of function. Recovery has been more rapid and more uneventful in our cases, than previously.

What we have said so far has concerned only reflexes mediated through the vagus. There are also reflexes mediated through the sym-

pathetic, which are constantly active, and tend to increase the coronary flow in response to increased needs. Failure of this normal vasodilator mechanism of the sympathetic, or an inhibition of the sympathetic, would necessarily result in an inability of the heart to adapt itself to its changing needs.

It has been known for a great many years that the pulse rate could be slowed by stimulation of the nasal mucous membrane in animals, and that this effect could still be obtained by the same stimulation after vagotomy or atropine, or both. The blood pressure might rise, or might remain unchanged. This can only be explained by assuming an inhibition of sympathetic tone.

These observations would seem to afford a possible explanation of the attacks of angina pectoris which occur when an anginous subject suddenly breathes cold air through the nose. Such attacks may even be fatal.

In order to determine if there might be a loss of sympathetic vasodilator tone in the coronary arteries, associated with what appears to be a sympathetic inhibition, experiments were done upon the decerebrate dog, in which the coronary flow was measured.[19] Upon stimulation of the nasal mucous membrane with cold water, or chloroform vapor, a decrease in coronary flow was observed, associated with a slowing of the pulse, and a rise in blood pressure. After vagotomy, or atropine, the same event occurred.

If ergotamine tartrate was administered to dogs in doses corresponding to those used clinically, for its sympathetic inhibitor effect, the same sequence of events occurred as was seen upon stimulation of the nasal mucous membrane. Vagotomy or atropine did not abolish this effect.

When experiments were done upon anginous subjects, inducing anginal pain by means of breathing a mixture low in oxygen, the pain was found to appear much sooner if ergotamine were administered before starting the experiment.

The experiments with ergotamine tartrate upon the dog, and upon the anginous subject are open to the objection that in each case the ergotamine tartrate may have exerted a direct vasoconstrictor action upon the coronary vessel walls. Katz[20] has shown such an effect in the empty beating heart of the dog and we have confirmed it. But I am not at all certain that these observations altogether settle the question of a direct action upon the vessel, and I would feel that much further work

is necessary. The curves representing the effects of stimulation of the nasal mucosa, where there is no question of any drug acting upon the vessel, and those obtained after the administration of ergotamine, are identical, and I would feel that this is of some significance.

The effect of tobacco upon the induction of anginal attacks has been commented upon frequently. Huchard[21] in his chapter upon Toxic Angina Pectoris, had a great deal to say about the effect of tobacco in causing attacks. Wilson and Johnston[22] recently reported a series of cases with what would seem very clear evidence that the anginal attacks were caused by a vasomotor narrowing of the coronary arteries, precipitated by the smoking. Hobbs, working upon this problem, has found two cases where the electrocardiographic changes did not occur after atropine.

I spoke earlier of the possibility that vasomotor restriction of coronary flow, oft repeated over long periods of time, might eventually result in permanent degenerative changes in the heart muscle consequent upon temporary decrease in blood supply. Blumgart and his fellow-workers[23] have shown that arrest of the blood flow for as short a period as one minute in a single coronary artery led to electrocardiographic changes indicating anoxemia of the muscle. Arrest of the flow for from 25 to 45 minutes produced histological changes in the muscle.

Hall, Ettinger and Banting[24] have shown that prolonged stimulation of the vagus, continued over several months of time, produced changes in the heart muscle of the dog, comparable to chronic clinical degenerative changes in man. Intrinsic changes in the vessel walls of the dog's heart did not occur to any significant degree. It would seem very reasonable to assume that similar changes occur clinically in man, or as a result of repeated extrinsic factors restricting the coronary flow for varying periods, over long time intervals.

The experiments of Hall and his associates were performed upon dogs with normal heart muscles and normal vessels. When the heart of man is hypertrophied from any cause, whether as a result of previous valvular damage, or as a result of hypertension, there is an increased bulk of heart muscle without a proportionate increase in blood supply to provide for the increased needs. In such hearts, with a blood supply already insufficient, or barely sufficient, and possibly with intrinsic vascular changes, a further restriction of coronary flow because of extrinsic

factors may produce serious changes much more rapidly and much more certainly than in a normal heart.

I am sorry to have burdened you with so long a discourse, but even then it is too brief and incomplete to show adequately the importance of the extrinsic factors which tend to decrease the coronary flow. I hope that what I have said has carried some small degree of conviction as to the importance of these factors in diagnosis and therapy.

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PULMONARY CONGESTION AND EDEMA*

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IN attempting to discuss the complex problem of pulmonary congestion and edema within the time allotted, I thought it advisable first to present certain general considerations and conclusions. Then I shall demonstrate these points more specifically with the help of lantern slides. The proposed discussion will be based mainly on experiences gained in the study of man. No attempt will be made to deal with the extensive and controversial animal experimentation.

Congestion and edema of the lungs are two important morbid states, which develop in the course of many diseases. Whenever they appear they are responsible for serious symptoms and for secondary complications. Thus, the majority of the symptoms and signs of congestive heart failure, such as dyspnea, orthopnea, cough, asthma, certain types of thoracic distress, cyanosis, rales, hemoptysis and hydrothorax, depend partly or entirely on such secondary derangements within the pulmonary circulation.[1]

It is only recently that the study of the normal and abnormal states of the human pulmonary circulation has become possible. As a result, valuable information has been accumulating not only on the pathologic physiology of the pulmonary circulation, but also on the better interpretation of structural alterations and of symptoms referable to the lungs.

The pulmonary (lesser) circulation may be looked upon as a counterpart of the capillary system of the greater circulation. As the huge capillary bed of the lungs is freely exposed to the atmospheric environment, it is not surprising that under certain conditions it undergoes serious disturbances. It is, indeed, remarkable that pulmonary edema does not develop under stress more frequently.

Usually the function of the blood capillaries is to send to or remove from the tissue fluids in which cells live, dissolved substances and fluids.

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Delivered during the Graduate Fortnight of The New York Academy of Medicine, October 23, 1941.

However, to a great extent the opposite is true, as far as the pulmonary capillaries are concerned. Their primary functional task is to allow the blood flow through the alveolar wall, while the respiratory exchange takes place, without change in fluids or solutes. This difficult homeostatic state of the pulmonary capillary circulation is maintained by a combination of physiologic and structural arrangements. Thus the relation of the low pulmonary capillary pressure to the osmotic pressure of the blood results normally, as far as the alveolar space is concerned, in a force of absorption, rather than of transudation. As early as 1873 Colin[2] demonstrated that as large an amount as 21 liters of water can be administered intratracheally to the horse in the course of three and a half hours without ill effects. Further, the pulmonary capillaries are unusual morphologically, in the sense, that they are "reinforced" by special layers of tissues which make diffusion of substances and transudation of the fluids difficult. Hence, although the minute vessels of the lungs are practically in contact with the air, nevertheless the blood is separated from the air by four delicate layers: (a) an endothelial layer, (b) two basement membranes, and (c) an epithelial layer. No lymphatic vessels or circulation exist within the alveolar walls, although the rest of the structures of the lungs are richly supplied with lymphatics. Actually the lymphatic network of the lungs is more dense and prominent than that of the liver, spleen, and kidneys. In view of the fact that conditions associated with edema of the alveolar wall are also associated with engorgement of the lymphatics and presumably with the lymphatic flow, it is assumed that the tissue fluids of the alveolar wall find their way to the lymphatics of the atria.

Under normal conditions the total cross-sectional width of the layers separating the circulating red blood cells from the alveolar air is less than one micron, hence gasses diffuse through the alveolar wall with ease. Each pulmonary capillary is about ½ to 1 millimeter in length and about 10 microns in diameter. Therefore, usually but a single row of red cells passes through the capillaries. As long as the alveolar wall remains elastic the pulmonary capillaries stretch easily. This is clearly indicated by the fact that histiocytes and large reticulo-endothelial cells, bulging with lipoid material, can pass through the normal pulmonary capillaries. Further, in heart failure with an increase of the pulmonary capillary pressure, the capillaries may enlarge 10- to 30-fold, and may assume aneurysmal dilatation. The surface of the pulmonary capillary bed has

been estimated at about 140 square meters (Hüfner). Under basal conditions about 3 to 3.5 liters of blood flow through the pulmonary capillaries per minute. In healthy persons the velocity of blood flow through the pulmonary circuit from the right to the left ventricle is 5 to 10 seconds, and anatomic and physiologic considerations indicate that the length of the pulmonary pathways is about equal. The average amount of blood at rest in the normal human lungs is about 500 to 800 cc. Under physiologic stress variations in the volume of blood flow and in its velocity *do not* parallel one another. In heart disease associated with pulmonary congestion there is a considerable degree of increase in the cross-sectional area of the capillary bed. Hence in these cases the disproportion between changes in the volume and velocity of the pulmonary blood flow is particularly great; and normal cardiac output may be associated with a slowing of over one hundred per cent of the normal velocity of the pulmonary blood flow. The shapes of dye concentration curves indicate that in the presence of pulmonary congestion caused by heart disease, in contrast to the normal pulmonary circulation, the velocity of blood flow varies in different parts of the lungs. It is considerably slower in the base than in the upper parts.

Neither the distribution nor the functions of the pulmonary nerves are clearly understood. The vagi and the sympathetic nerves form numerous plexuses and nerves along the bronchial tree and pulmonary vessels. According to Miller,[3] the nerves end in the walls of the atria and in smooth muscles of the smallest bronchioles. Olkon and Joannidas[4] and Sternberg and Tamari,[5] on the other hand, have claimed that the capillaries of the lungs are innervated. It is doubtful whether the pulmonary capillaries are under active nervous control, in the orthodox sense. Chemical agents, on the other hand, liberated by nervous stimulation, may well influence the capillaries directly or indirectly.

The physiologic mechanism as well as the treatment of pulmonary edema is *not uniform* in all cases. The usual clinical causes of pulmonary congestion and edema are: (a) changes in the pulmonary circulation caused by heart failure (coronary disease, arterial hypertension, aortic insufficiency or stenosis, mitral disease and diffuse myocardial disease); (b) systemic or pulmonary diseases associated with pronounced changes in the pulmonary hemodynamics and/or with capillary damage (pulmonary infarcts, pneumonias, drowning, irritant gasses); (c) diseases associated with retention of fluids in the tissues (beriberi, glomerulone-

phritis, and toxemia of pregnancy). Frequently in the causation of pulmonary edema the physiologic causes are combined. Such is the case in certain instances of pneumonia, beriberi, uremia, toxemia of pregnancy, thyrotoxicosis and circulatory shock. It has been known for a long time that certain diseases of the central nervous system (cerebral trauma, cerebrovascular accidents, and encephalitis) are frequently associated with pulmonary edema. The pathogenesis of this edema is not clear. It is probable that in these so-called "neurogenic" pulmonary edemas, the underlying mechanism is a disturbance of the vasomotor system with secondary changes in the functional capacity of the heart, in the greater and in the pulmonary circulation. In this sense neurogenic factors induce pulmonary edema indirectly.

In general it may be said that *the formation of pulmonary edema follows the same biologic laws as the development of peripheral edema;* although the relative significance of the factors involved is apparently not the same in these two types of edemas. Changes in capillary pressure, blood flow, protein content of the blood, permeability of the capillary membranes, are the chief factors operative in the formation of pulmonary edema. Combination of high capillary pressure, stasis (ischemia) and anoxia are particularly important in the causation of pulmonary edema of heart disease. It is probable that in slow blood flow, the active factors are chemical in nature. Specific evaluation of factors causing changes in the permeability in the pulmonary capillary wall is particularly difficult; but in this respect again the situation is not unlike that in the capillaries of the greater circulation. It appears that if once the activity of causative factors reaches a certain critical point, edema formation can progress with great rapidity. The longer the duration of the pulmonary edema, the more difficult it becomes to reëstablish the normal physiologic state. The edema fluid may be of low or high protein content. As a rule the edema fluid of cardiac origin is low in proteins (transudate), while that caused by infections or of chemical origin is high (exudate). As histologic observations have shown, the pulmonary capillaries are relatively easily permeable to red and white cells. The edema fluid both of the alveolar space and of the lymph frequently contains red cells. Pulmonary edema may be acute or chronic. Acute pulmonary edema may be transient or fatal. Both pulmonary congestion and edema may be diffuse or localized. One of the best examples of localized pulmonary edema is that occurring in pneumonia. This

type of edema is caused by gross damage done to the capillary layers by the bacteria. The high protein content of alveolar fluid indicates that here we are dealing with an inflammatory exudate.

In heart disease congestion usually precedes pulmonary edema. The edema may be either *pericapillary (interstitial)* or *intra-alveolar*, or a combination of the two. Usually, however, the intra-alveolar edema of heart disease is preceded by pericapillary edema. The pulmonary edema caused by infectious diseases, chemical agents and perhaps nervous mechanisms, on the other hand, often develops without any preceding congestion, and results instead from changes in the permeability of the layers of the alveolar wall ("primary" intra-alveolar edema).

On the basis of studies conducted in man during the past fifteen years,[1, 6-21] an attempt has been made to correlate symptoms, physical findings, and roentgenological characteristics, with physiologic and histologic findings. A few of the pertinent conclusions are as follows:

1. Failure of the pulmonary circulation occurs frequently in the presence of an adequately maintained greater circulation. Thus, dyspnea, orthopnea, pulmonary edema, and low vital capacity of the lungs can be associated with normal cardiac output, normal arterial and venous pressure, and normal utilization of oxygen by the tissues.

2. Pulmonary engorgement is usually associated with some degree of edema of the alveolar wall, causing thickening and rigidity of the alveolar sac. If the edema has existed for but a short period, rapid reabsorption of the edema fluid develops provided the normal physiologic relationships are reëstablished. Measurements of air spaces in cardiacs with acute pulmonary congestion indicate that changes in the lungs are responsible for the creation of an acute functional emphysema-like state.

3. Pericapillary edema of the alveolar wall can lead rapidly to deposition of collagen. Judging from the behavior of the lungs in preëclampsia and eclampsia of pregnancy, collagen may be deposited in the edematous alveolar wall over a period of weeks, and subsequently, presumably, this collagen can become absorbed. If, however, the edema persists, permanent organic changes can occur in the alveolar wall. The advanced manifestation of the structural changes consists of fibrosis of the alveolar wall with obliteration of the capillary bed and with cuboidal changes in the epithelial cells. Thus, heart disease can cause first physiologic (reversible) and subsequently organic (irreversible) lung disease. The latter is seen in advanced cases of mitral stenosis. In these patients, not

only are the capillaries markedly widened, but the alveolar wall is considerably thickened. This is the chief cause of central (pulmonary) cyanosis in these patients. In some cases with an advanced type of mitral stenosis rupture of the capillaries with aneurysmal enlargement can be responsible for serious and at times fatal pulmonary hemorrhage.

4. In the presence of an advanced degree of mitral stenosis, dilatation of the pulmonary capillaries over the upper half of the lungs may not be accompanied by an appreciable degree of pericapillary edema. This observation suggests that increased intracapillary pressure alone, without slowing of the blood flow or anoxia, is not necessarily the primary factor in the causation of pulmonary edema.

5. A large amount of pericapillary (interstitial) edema may be present in the lungs without intra-alveolar edema and without pulmonary rales. This situation is responsible for the clinical fact that patients with left ventricular failure, in particular, can have dyspnea, orthopnea and low vital capacity of the lungs without rales.

6. In primary intra-alveolar edema the structure of the alveolar wall remains normal, and yet intra-alveolar filtrate diffuses freely through all layers of the alveolar wall. At times, with the edema fluid, large numbers of red cells pass through the alveolar wall. The physical signs of this type of edema consist of extensive bubbling rales. Diffuse intra-alveolar edema may be unilateral or may involve but one lobe.

7. The term "left ventricular failure," or more properly "chronic left ventricular failure," does not imply that under usual conditions the output of the two ventricles is unequal. This would be a physiologic impossibility. These terms simply indicate that there is severe impairment of the reserve of the functional capacity of the left ventricle as compared with that of the right ventricle. As a result, under *physiologic stress*, serious imbalance between the functions of the two ventricles is prone to occur. In the understanding of paroxysmal dyspnea (cardiac asthma) and transient pulmonary edema associated with heart disease, it is essential to appreciate that a disproportion in the functional activities of the two ventricles can lead to active engorgement and gross disturbance of the pulmonary circulation within a few seconds or minutes. If following such temporary imbalance, the vitally essential balance between the ventricles, as far as equal output of blood is concerned, is reëstablished, the engorgement accompanied by dyspnea, orthopnea, and edema will, nevertheless, continue to persist, because the previously

accumulated excess of blood and edema now remains trapped within the pulmonary circuit. Under such circumstances for the relief of the attack, it is essential that the left ventricle temporarily throw out more blood from the lungs than the right throws in. Otherwise, the excess volume within the pulmonary circuit has to diffuse into the lung tissues, lymphatics, and alveoli, before the dyspnea and orthopnea will disappear. Most effective measures in the treatment of acute left ventricular failure with dyspnea, asthma, and pulmonary edema bring about temporary improvement in the function of the left ventricle. This is accomplished by decreasing either the arteriolar resistance or the inflow to the heart or both. Studies conducted by us indicate that improvement in the pulmonary circulation is often accomplished promptly, while disappearance of edema and stiffening of the lungs, takes a longer time. We have observed both in patients with cardiac asthma and in those with other types of heart disease, that the restoration of the pulmonary hemodynamics long preceded the disappearance of the so-called "functional circulatory emphysema" caused by changes within the alveolar wall proper.

8. Acute left ventricular failure or transient disproportion between the two ventricles, may be associated with normal, elevated, or low arterial pressure of the greater (peripheral) circulation. It is particularly important to realize that the syndrome of acute heart failure or "cardiac shock" is accompanied by a clinical picture similar to or identical with that associated with acute circulatory collapse or shock of peripheral vascular origin. Thus, in cardiac shock such as occurs in coronary thrombosis, pulmonary edema depends on failure of left ventricular function, notwithstanding the fact that the arterial pressure is low and the clinical picture is one of shock.

9. In some instances of left ventricular failure caused by arterial hypertension, attacks of paroxysmal dyspnea are associated with acute pulmonary engorgement and with progressive histologic changes such as deposition of fibrin and connective tissue, which in the past have been erroneously looked upon as "organising pneumonia."

10. Attacks of pulmonary edema may be associated with fever and leukocytosis, the latter reaching as high a degree as 40,000 white blood cells per cmm. of blood. Patients have been observed, in whom each attack of paroxysmal dyspnea has been associated with fever of one to three days duration.

11. Roentgenologic studies of pulmonary congestion and edema indicate that the distribution of edema varies in different types of congestive failure. In "general" failure of the heart, the congestion and edema are usually dependent ("basal")—(passive engorgement). In pure left ventricular failure, the congestion and edema are often hilar and perihilar, with progressive fan-shaped distribution (active engorgement). The base of the lungs often remains relatively normal. It is of interest, that usually the congestion and edema start over the right lung and remain more intense over this side. This is significant in view of the fact that right hydrothorax usually precedes left hydrothorax.

12. During and immediately following an attack of cardiac asthma or pulmonary edema, as shown by roentgenograms, various bizarre-shaped distributions of edema can appear. These changes may disappear within 24 to 48 hours. Obstruction of lymphatic drainage is one factor which influences the persistence of edema within certain areas of the lungs. At times the appearance of the roentgenogram may be similar to or identical with that observed in tuberculosis or pneumoconiosis.

13. Accumulation of edema in the large lymphatic vessels close to the lung roots can be responsible for a large cyst-like accumulation of fluid, imitating the shadows caused by aneurysms or neoplastic diseases.

14. In rare instances of mitral stenosis small, persisting, diffusely-scattered, dense areas are present in roentgenograms of the lungs. Such a roentgenogram imitates that found in miliary tuberculosis or in sarcoid. The areas described are formed by hemosiderin pigment deposits and surrounding tissue reactions.

15. The roentgenologic differentiation of pulmonary edema, infarction, pneumonia and fibrosis is often difficult. Pulmonary infarction is often associated with local or generalized pulmonary edema.

16. In the treatment of pulmonary edema the specific pathogenesis is to be taken into consideration. In the usual paroxysmal dyspnea and edema of cardiac origin factors which relieve pulmonary engorgement and stasis and improve the functional capacity of the left ventricle are the effective measures.

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OXYGEN SUPPLY SYSTEMS FOR MILITARY FLYING*

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IN preparation for writing this paper, I took occasion to refer to an article which I read nearly nine months ago. As a matter of fact, it has not yet been published. In it I presumed to define in some detail the requirements of military oxygen supply apparatus in conformity with the necessity of meeting the requirements of the airplane, the service and the personnel.

The principles expressed at that time are as sound today as they were then but in re-reading it a few days ago, I was astonished at the progress which has been made since then. There was no intent then to create the inference of prophesy but, in retrospect, development of oxygen equipment and description of desiderata for such equipment have followed very closely the principles which were generally accepted then. Nor were the general principles then expressed considered as the implantation of seeds for the fruition which is presently to be garnered. Nevertheless, it is timely to describe equipment as it exists or is being developed today and to reiterate requirements in much more exact terms than was possible that short time ago.

The credit for the advances made cannot be given to any single individual or group of individuals. Contributors include service personnel, private research groups, federal agencies and the industry itself. No small measure of credit is due the National Research Council's Committee on Aviation Medicine. A far-sighted, comprehensive plan for investigation, a thorough knowledge of goals to be attained and the methods to be employed in reaching them, an unremitting zeal in adding to their knowledge by all possible means and an unstinted patriotic application of time and effort have done much to make our present status what it is. Itself without funds, the National Research Council's Committee on Aviation Medicine has guided and urged other better endowed agencies in their efforts. Specifically, the formulation of desiderata and criteria

* Read before The New York Academy of Medicine, November 6, 1941.

for testing proposed oxygen equipment is a direct and distinct contribution of the Committee.

Before beginning a detailed description of the types of oxygen equipment for military flying, it may be well to review briefly the reasons for its use. For this purpose, I have decided to show two charts which illustrate the cardinal reasons for the use of oxygen and the special requirements interposed for military aviation.

Chart I shows very graphically in parallel column the important meteorological conditions encountered in ascending to higher altitudes.

Chart II shows the total barometric pressure prevailing at increasing altitudes, the partial pressure of oxygen at normal percentage at those altitudes, the arterial saturation under these partial pressures and the arterial saturation at these altitudes when 100 per cent oxygen is breathed.

It will be noted that while breathing normal air the arterial saturation is significantly reduced even at 10,000 feet and is progressively reduced as the altitude increases. At 20,000 feet the arterial saturation is only 60 per cent. This shows why normal efficiency cannot be expected at this altitude breathing normal percentages of oxygen.

When the deficiency in partial pressure using normal percentages is made up by providing 100 per cent oxygen in a breathing apparatus, the arterial saturation continues to be adequate for physical and mental efficiency up to 30,000 feet at least. However, please note that as we approach 40,000 feet, the total barometric pressure drops so low that, even if the inspired mixture is made up of nothing but oxygen, its partial pressure is inadequate to preserve 100 per cent arterial saturation. Above these altitudes, arterial saturation can only be maintained by raising the total barometric pressure by pressurizing cabins or suits.

But replacing the deficiency of oxygen to avoid anoxia is not the complete picture. In addition to the problem of anoxia, per se, we are beset by the ogre of aeroembolism which rears its ugly head in increasing ferocity. With increasing rates of climb to higher and higher altitudes and capability of continuing at these altitudes for increasingly longer periods of time, we find that the contribution which oxygen supply apparatus can make to the solution of this problem becomes increasingly important. Without discussing aeroembolism in any detail, suffice it to say that the only practical solution we have today is the augmentation of nitrogen elimination provided by breathing pure oxygen for

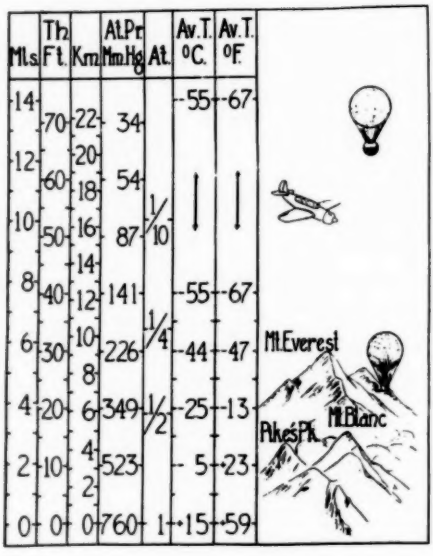

Chart I

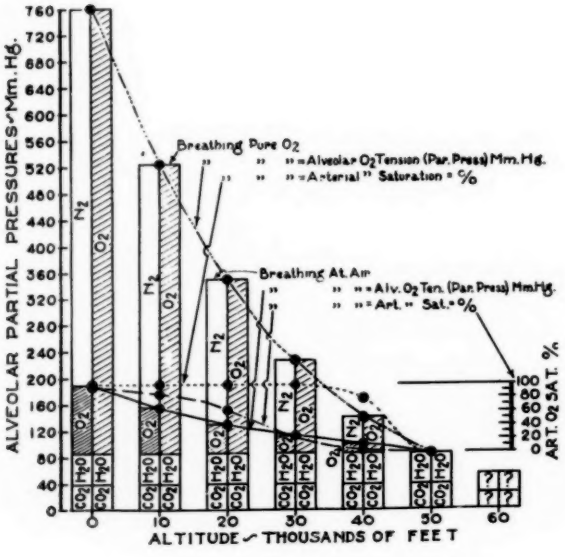

Chart II

as long as possible before attaining 30,000 feet. This means, for the purposes of this evening's discussion, that for military missions in which aeroembolism is a hazard, oxygen equipment must be capable of delivering 100 per cent oxygen from time of take off.

This brings us to the description of the types of oxygen equipment which can find application in military aviation. In the first place, it is well to reiterate that it appears undesirable to settle upon a single type of apparatus for all purposes. This is apparent by considering the wide range of variations in the need to which military aircraft are put.

On the one extreme is the very fast, rapidly climbing high altitude interception fighter. Those small planes can take their pilots to altitudes at rates which make aeroembolism an important likelihood. But their total time in the air may not exceed two hours. Oxygen must be supplied these pilots completely unadulterated from the ground up, from before take off. The nature of the mission precludes any adjustment or attention during the flight. They must be positive, simple and generously adequate. The whole flight will require but a relatively few liters of oxygen under constant flow conditions. It may be that the most practicable and reliable means of supply for this type is a constant flow system which provides a positive pressure at the face, thus reducing the necessity for close fitting masks.

At the other extreme are the long range patrol bombers with a multiple crew, never or seldom attaining to extreme altitudes yet flying for long periods at moderate oxygen altitudes. In this type, economy of oxygen is of the essence. Aeroembolism is not a problem. The crew is large enough to permit considerable frequent and delicate adjustment. Adjustment must be capable of providing for the range of activity between sedentary co-pilot and ammunition-wrestling gunners. Most of the crew may be comfortably warm. An exposed bombardier or gunner may be exposed to extremely low temperature on occasion. For this type, we may find a place for elaborate installation with facilities to adjust for wide ranges of physical exertion and altitudes, designed and operated on the basis of a cardinal need for economy.

Between these extremes there are variations in types of aircraft where oxygen installation must be judged on the basis of rate of ascent, to what altitude, for how long a flight, with what degree of exertion or cold and with what opportunity for adjustment and control of equipment. Indeed, it appears unreasonable to expect a single type of equip-

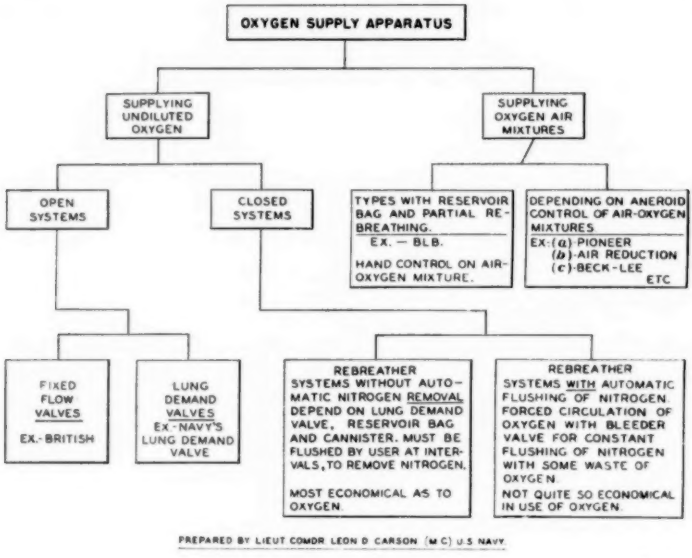
OXYGEN SUPPLY APPARATUS
SUPPLYING UNDILUTED OXYGEN
SUPPLYING OXYGEN AIR MIXTURES
OPEN SYSTEMS
CLOSED SYSTEMS
TYPES WITH RESERVOIR BAG AND PARTIAL RE-BREATHING.
EX. — B.L.B.
HAND CONTROL ON AIR-OXYGEN MIXTURE.
DEPENDING ON ANEROID CONTROL OF AIR-OXYGEN MIXTURES
EX:-(a)-PIONEER
(b)-AIR REDUCTION
(c)-BECK-LEE
ETC.
FIXED FLOW VALVES
EX.-BRITISH
LUNG DEMAND VALVES
EX.-NAVY'S LUNG DEMAND VALVE
REBREATHER
SYSTEMS WITHOUT AUTOMATIC NITROGEN REMOVAL DEPEND ON LUNG DEMAND VALVE, RESERVOIR BAG AND CANNISTER. MUST BE FLUSHED BY USER AT INTERVALS, TO REMOVE NITROGEN.
MOST ECONOMICAL AS TO OXYGEN.
REBREATHER
SYSTEMS WITH AUTOMATIC FLUSHING OF NITROGEN. FORCED CIRCULATION OF OXYGEN WITH BLEEDER VALVE FOR CONSTANT FLUSHING OF NITROGEN WITH SOME WASTE OF OXYGEN.
NOT QUITE SO ECONOMICAL IN USE OF OXYGEN.
PREPARED BY LIEUT COMDR LEON D CARSON (M C) U.S NAVY.

Chart III

ment to meet all requirements without some sacrifice somewhere. The analogy may be far fetched but the situation might be compared to installing the same motor in a jalopy and in a 10-ton truck. But it is equally true that there are many reasons for keeping the number of types at a minimum. Procurement, maintenance, indoctrination, familiarity, serviceability and uniformity all point to the desirability of a very limited number of types. The balance between these two concepts must be struck on a fulcrum which is ever changing as types of aircraft and tactical uses vary in relative concentration. The range of choice is apparent when we consider the types of equipment available.

Oxygen supply apparatus are divided, first, into (a) those which supply undiluted oxygen and (b) those which supply oxygen and air mixture.

Undiluted Oxygen Systems

Those supplying undiluted oxygen are divided into (1) open systems and (2) closed systems.

Open Systems

The open systems are by far the least economical of oxygen. They are the most dependable to furnish 100 per cent pure oxygen. In one case, the oxygen is supplied by fixed flow valves with no control over rates of flow. These provide a constant flow of pure oxygen through the breathing mask. They do not require expiratory leak-proof masks, have no valves to provide resistance to breathing, are not so subject to freezing as those with expiratory valves, are very reliable and are very simple in construction and operation. They are very wasteful of oxygen. In another case, operation depends upon the lung demand principle. A system of valves is incorporated to permit the flow of oxygen only during inspiration. During expiration and the pause between expiration and inspiration, the supply of oxygen is cut off. Because of this intermittent flow, this type is more economical than the fixed flow valve type but it makes no provision for the percentage of oxygen not absorbed by the lungs, more than 85 per cent oxygen being exhaled to the open air.

The lung demand type interposes a number of stipulations which require very careful control and test criteria. They must function throughout a wide range of barometric and temperature variation. They must provide adequate partial pressure of oxygen up to the physiological ceiling. They must be capable of furnishing adequate rates of flow even under extreme exertion and peaks of inspiratory demand. They depend on both inspiratory and expiratory valves which must introduce a minimum resistance and must not freeze at very low temperature and moderate wind velocities. The lung demand type requires an absolutely leak-proof mask. If there is an inspiratory leak there will be dilution by ambient air. If there are expiratory leaks, there is increased chance for frostbite and loss of economy through failure to close the lung demand valve. They must be provided with emergency by-passes. The number and exactitude of these stipulations has prompted the National Research Council's Committee on Aviation Medicine to formulate an extensive set of desiderata and test criteria. If time permitted, it would be interesting to describe these in detail.

Closed Systems

The closed systems for supplying undiluted oxygen are essentially

rebreathers which provide for conservation of unabsorbed exhaled oxygen. There are two general types. In one the system is entirely closed except for a manually operated exhaust valve. Exhalation is through a cannister which absorbs oxygen and moisture (and incidentally generates a small amount of oxygen) into the breathing bag. As the rebreathing volume is depleted by absorption of oxygen in excess of that generated, the deficiency is made up by the opening of a valve from an oxygen supply system. This may be an integrally attached flask or a central low pressure supply system which may be tapped at a number of positions distributed throughout the aircraft. This is by far the most economical of all oxygen breathing apparatus. It has one significant drawback. There is no provision for automatic exhaustion of nitrogen which accumulates in the system during ascents. As the ambient barometric pressure decreases, nitrogen will appear out of solution in the cells, tissue fluids and blood into the expired air. Even though no nitrogen is introduced from the outside into the completely closed system as much as a liter may accumulate in the breathing circuit in an ascent to 18,000 feet. This accumulated nitrogen is disposed of by periodic flushing of the entire system by exhalation through the manually controlled exhaust valve. This requires conscious attention on the part of the user because there is no means of knowing the exact amount of dilution by oxygen. Also, as ascents are made to higher altitudes there will necessarily be dilution by nitrogen and this system has, therefore, a "built-in ceiling."

Another type of rebreather provides for the elimination of nitrogen by constant bleeding of a portion of the rebreathing volume. For this reason it is not so economical as the completely closed circuit type. The oxygen is forcibly circulated by an injector in the oxygen supply line. It circulates under slight positive pressure past the bleeder valve through a carbon dioxide absorbent, thus maintaining a high percentage of oxygen. Tidal air variations are provided for by a breathing bag. Preliminary tests of a model of this type gives considerable promise of its efficiency and adaptability to military flying.

Both types of rebreather have one common, very desirable feature. They supply warm oxygen. The chemical action of the carbon dioxide absorption produces considerable heat which extends into the inspired portion. At altitudes where the temperatures are low, this is a tremendously comforting thing for the user.

By the same token, they have one common serious impediment. They will not start at low temperature. No carbon dioxide absorbent will begin action in the presence of cold dry carbon dioxide alone. If the apparatus becomes chilled by not being used before cold altitudes are encountered or by climatic conditions, the exhaled moisture will condense before the exhaled oxygen and carbon dioxide reaches the absorbent. Under these circumstances the chemical reaction involved in the absorption of carbon dioxide will not begin spontaneously. This can be obviated by exhaling directly into the absorbing cannister or by artificially heating the exhaust tubing. Both of these introduce engineering and service complications. Nevertheless, the promise of economy of oxygen in the rebreather type of oxygen equipment warrants accelerated efforts to overcome this impediment.

Oxygen-Air Mixture Systems

In the interest of economy, a number of oxygen breathing apparatus have been and are being developed on the general principle of permitting dilution by air at altitudes at which 100 per cent oxygen may be unnecessary. These are mentioned in the first division in contrast to those supplying undiluted oxygen. Here, again, we find a dichotomy into those which incorporate anaeroid control of the amount of dilution by ambient air and those which depend upon varying rates of flow to provide an adequate concentration of oxygen.

Anaeroid Control Type

The anaeroid control type is essentially a lung demand type which permits decreasing dilution of ambient air up to a minimum altitude above which only 100 per cent oxygen is acceptable. For the kinds of flying to which this type is adapted, it need not supply oxygen under 8,000 feet but must supply pure oxygen at 25,000 feet and over. Within this range the increments of oxygen and air may vary, being governed on the one hand by a minimum partial pressure of oxygen of 70 mm. mercury and on the other hand by economy of oxygen.

Several models of this type of equipment are being developed and tested. They vary in certain details such as anaeroid control of the oxygen supply, the air supply or both; methods of mixing; reduction of pressure from high or low pressure supply lines; means of providing for peak inhalations, etc., but, essentially, they embody the same general

principles. To find wide or general applications, they must be provided with means to shut off the dilution and supply pure oxygen at all barometric pressures.

Rate of Flow Control Type

Any type of diluter supply system which depends upon varying rates of flow of oxygen to a breathing bag to provide for adequate concentration of oxygen at varying altitudes and exertion and does not incorporate either manual or automatic means for controlling the amount of air intake, has certain basic fallacies. If the rate of flow is adequate to provide for high altitudes and moderate exertion, it becomes essentially a free flow apparatus and economy is lost. If the amount of air dilution is unknown or unpredictable it will expose the user to the insidious influence of anoxia which may become poignant at any time as a sudden and catastrophic collapse.

This discussion is purposely avoiding inclusion of the different means of supplying oxygen to the aircraft, whether liquid or gaseous, high or low pressure flasks or hypothetically possible means of generation or compressing in the aircraft. These are essentially engineering problems. Two cardinal requirements must be observed: the oxygen must be pure and it must be dry. A detailed discussion of oxygen masks and helmets has also been scrupulously avoided. This subject is too interesting and intriguing to be sketchily included in this paper which has already consumed too much time.

Types Being Used

Just a word about the types being used by air services today. From information which reaches us through liaison channels, it may be said that, in general, European combatants are using models of the following types of equipment: The R.A.F. is using a type of free flow apparatus which can be adjusted for different altitudes and does not require a leak-proof sealed mask. They are making rapid progress in the development and extension to service of more economical equipment, better fitting masks and means for providing oxygen. The Luftwaffe has profited by their years of peace-time preparation and has the best equipment in service use today. They have concentrated on a lung demand type which is characteristically well designed and built, is very efficient and foolproof, has been perfected by years of meticulous research and

extreme service proving and could be profitably copied by any air service. In our service we are well equipped with oxygen apparatus. The Navy uses a lung demand type and the Navy rebreather. They are quite satisfactory. The Army Air Forces are using a rate of flow regulator which is meeting service needs.

We have had an excellent year of accelerated research, development and testing of improved oxygen equipment. In a subject as important as oxygen supply apparatus for military aviation, there should be no let-up in this program of improvement.

Tremendous strides have been made, thanks to the characteristically American kind of all out service of brains, sweat, ingenuity and productivity. We are prepared to write the detailed specifications for the immediate mass production of the best types of oxygen equipment to meet the needs of our growing flying services. Those who have contributed to this development and have made our confidence justifiable, have every reason to be genuinely proud.

SOME RECENT ADVANCES IN DRUG THERAPY*

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THE subject for discussion this afternoon is "Some Recent Advances in Therapeutics." It was decided that such an assignment could be turned to the best advantage of the listeners by reviewing the majority of important therapeutic advances rather than by selecting only a few topics for detailed discussion. In addition to answering the perennial question, "Well, what is new?", an attempt will be made to answer the more important query, "What is it worth?" With this plan in mind, it is of interest to survey briefly the newer advances in drug therapy by arranging them in groups according to their relative clinical value. For the purpose of the present discussion, new drug therapies, or new ways of employing old drugs, have been arranged in four groups—according to the following scheme: In Group I are included those advances which are now generally accepted and of proven worth. In Group II are listed those advances which are very promising, but which require further clinical investigation before being widely employed in daily practice. In Group III are placed what, in the reviewer's opinion, are questionable therapies, requiring further work to delineate their proper status. In Group IV are listed those therapies which, in the reviewer's opinion, either hold very little promise, or which are irrational and destined for eventual discard. Some medical toes are bound to be tread on in attempting any such classification as this, and it must be emphasized that the selection is purely one person's appraisal. It is to be regretted that a detailed presentation of the reasons underlying each particular classification cannot be given here.

GROUP I

In Group I are tabulated those recent advances in drug therapy of

* Delivered at The New York Academy of Medicine, November 7th, 1941, in the Friday Afternoon Lecture Series.

TABLE I

RECENT THERAPEUTIC ADVANCES OF PROVEN WORTH

Newer sulfonamides (sulfadiazine, sulfaguanidine)	Antispasmodic atropine substitutes (syntropan, trasentin, etc.)	Dihydrotachysterol (in parathyropriva)
Local use of sulfonamides	Thiamine (in deficiency neuritis, C-V states, ophthalmoplegia)	Desoxycorticosterone (in Addison's disease)
Prophylactic oral use of sulfonamides	Nicotinic acid (in pellagra, deficiency encephalopathy)	Quinine (in myotonia congenita)
Dilantin (in epilepsy and in psychic equivalents)	Riboflavin (in deficiency cheilosis, keratitis)	Papaverine (in peripheral and pulmonary arterial embolism)
Blood substitutes (human plasma)	Vitamin K (in hemorrhagic diatheses due to a prothrombin deficiency)	Heparin (in blood vessel surgery; to prevent thromboses and embolism; etc.)
Newer epinephrine preparations (inhalation, 1%; oil solution, 0.2%)		
Theophylline ethylene diamine (in bronchial asthma)		

proven worth which are to be recommended for use in daily practice (Table I).

Newer Sulfonamide Therapy. At the head of the list appear the newer sulfonamide therapies. These have been so adequately dealt with in the current literature that it is not intended here to discuss them in any detail. *Sulfadiazine* and *sulfaguanidine* are the latest valid additions to the sulfonamide family. The *local* use of the entire group has come into considerable prominence within the last year and the value of this local therapy for medicine and surgery is difficult to exaggerate. Somewhat overshadowed is the fact that there are certain valid *prophylactic* uses for *oral* medication with sulfonamides, including the following conditions or diseases: the quiescent stage of rheumatic fever, scarlet fever contacts when the Dick test is positive, meningococcus carriers, compound fractures, extensive tissue injuries, peritonitis, otitis media, and burns, and prior to resections of the large bowel, urological operations, etc. With these sketchy remarks, respect has been paid to the most important advance of the century, and other drug therapies may now be considered.

Dilantin in Epilepsy. Dilantin has become firmly and deservedly entrenched in the treatment of epilepsy since its introduction in 1938, and possesses two outstanding advantages. First, dilantin is not a seda-

tive. Secondly, in addition to being at least as effective as bromide, phenobarbital, or the ketogenic diet in the control of grand mal, it is much more effective in the management of seizures of the psychomotor equivalent variety. Therapy with phenobarbital or bromide, as a rule, does not improve and may even aggravate symptoms in patients with psychic equivalents.

Human Plasma as a Blood Substitute. Of all the substitutes for human blood, the best is undoubtedly human plasma, either stored as such, or dried by the lyophilic method. Plasma is especially useful in the treatment of surgical and traumatic shock, in burns when loss of available plasma occurs, to combat hypoproteinemia, and as a temporary substitute for whole blood in hemorrhage, when whole blood is not immediately available. The plasma from different donors may be pooled and blood grouping of the recipient is then not necessary.

Newer Preparations of Epinephrine. In the symptomatic treatment of allergic states, and especially in bronchial asthma, the newer preparations of epinephrine have been of considerable assistance. These include the strong solution of epinephrine (1:100), inhaled after nebulization, and the solution of epinephrine in oil (1:500), injected subcutaneously or intramuscularly for prolonged therapeutic effects.

Theophylline in Bronchial Asthma. Not yet fully appreciated is the fact that within very recent years theophylline has been established as an effective bronchial antispasmodic. The mechanism of action of the drug is a direct spasmolytic effect on the bronchial smooth muscle. In asthma, it is usually administered by mouth for prophylactic purposes, or for control of symptoms in cases of moderate severity; but the drug often produces dramatic relief of status asthmaticus when injected intravenously. Theophylline with ethylene diamine, commonly known as aminophylline, is the preparation used for parenteral administration. This drug deserves wider clinical trial.

Synthetic Atropine Substitutes. Among the synthetic substitutes for atropine are several valuable antispasmodics—including novatropine, eumydrine, syntropan and trasentin. These are not exactly new drugs but only within the last two or three years has their clinical usefulness become generally appreciated. Novatropine and eumydrine retain much of the atropine structure, but syntropan and trasentin are more closely allied to the local anesthetics and actually have local anesthetic potency. Indeed, one may wonder whether the rapid relief of pain reported to

occur when these two compounds are given orally to patients with peptic ulcer may not, in some measure, be due to a local anesthetic action. All four agents have been found effective as antispasmodics and one or the other has been successfully employed in the symptomatic treatment of a variety of clinical conditions, including the following: pyloric stenosis in infants, spastic dysmenorrhea, ureteral colic, urethral spasm, hypertonic urinary bladder, spastic dyskinesia of the gall bladder and biliary ducts, and gastrointestinal spastic states. The common denominator of all these conditions is smooth muscle spasm. The agents mentioned relax the spasm without producing the unpleasant effects of atropine or other belladonna alkaloids, such as dry mouth, mydriasis, and changes in cardiac rate. In other words, more discrete therapeutic results are obtained. Syntropan and trasentin, in particular, produce their therapeutic effects by acting more directly on smooth muscle rather than by blocking cholinergic nerve impulses to smooth muscles. Before leaving this topic, it might be mentioned that quite recently certain obstetricians have been employing syntropan experimentally in labor, on the basis that dystocia of maternal origin is commonly due to functional spasm of the cervix, and that the drug might hasten cervical dilatation. Preliminary results obtained on several hundred patients indicate that labor may be shortened in duration by as much as 50 per cent, both in primipara and multipara, and apparently without deleterious effects on mother or infant. Obviously, this work requires careful study and confirmation before its status can be decided.

Thiamine. Thiamine, or vitamin B_1, is important in human nutrition. However, as a *therapeutic* agent, it should be employed chiefly when a definite deficiency is present, as in frank beriberi, in deficiencies characterized by certain forms of cardiovascular or gastrointestinal disorders, in symmetrical peripheral neuritis due to a lack of the vitamin and in Wernicke's ophthalmoplegia.

Nicotinic Acid. Nicotinic acid, another member of the vitamin B family, is similarly important in nutrition. However, as a *therapeutic* agent, it too should not be employed except in the presence of a specific and clear-cut nicotinic acid deficiency. As far as known at present, this occurs only in pellagra, and in an encephalopathy due to a deficiency of the vitamin.

Riboflavin. Riboflavin, another constituent of the vitamin B complex, is also essential in human nutrition. As a *therapeutic* agent, it should

be employed only when a definite deficiency is present. As far as is now known, such a deficiency of riboflavin manifests itself in man only in certain types of cheilosis, and in ocular disturbances consisting chiefly of a vascularizing keratitis, photophobia and impairment of visual acuity.

Vitamin K. Vitamin K is essential in human nutrition because of the role it plays in the production of prothrombin. In preventing or curing hemorrhagic diatheses due to hypoprothrombinemia, substances possessing vitamin K activity share qualitatively the same mechanism of action in elevating the plasma prothrombin. These substances are employed both prophylactically and therapeutically. In general, vitamin K is useful only in those hemorrhagic conditions in which abnormal bleeding is due to a low concentration of plasma prothrombin that is not occasioned by hepatic cell injury. This limits the employment of the vitamin to the hemorrhagic diatheses of certain types of hepatic and biliary disease, and to rarer instances of deficiency caused by faulty diet or absorption defects of the intestine other than those caused by a loss of bile. Vitamin K is employed prophylactically in all jaundiced patients in whom surgical procedures are planned, and also postoperatively if the prothrombin level was low before operation. Vitamin K is also a valuable agent in the treatment of hemorrhagic diseases of the newborn, and its administration to pregnant women prior to delivery has become routine. The commonly employed synthetic vitamin K preparation, 2-methyl-1, 4-naphthoquinone has been given the non-proprietary name "menadione" by the Council on Pharmacy and Chemistry of the American Medical Association.

Dihydrotachysterol in Parathyropriva. Dihydrotachysterol is a drug derived during the progressive irradiation of ergosterol. It is closely related to vitamin D. Within recent years, it has proven to be definitely useful in the management of patients with parathyropriva, having the advantage of being effective after oral administration. It is thought to exert its beneficial effect in raising the serum calcium and lowering the serum phosphorus through a mechanism of action similar to that of parathyroid extract.

Desoxycorticosterone in Addison's Disease. Desoxycorticosterone, one of the several adrenal cortical hormones, has proven of great value in the treatment of patients with Addison's disease, but its use necessitates considerable attention to the intake of sodium in order not to increase blood volume and thereby tax the circulation. It also appears

that desoxycorticosterone does not correct the defect in carbohydrate metabolism which exists in adrenal cortical insufficiency. For this reason, it may be necessary at times to supplement desoxycorticosterone with crude extract of the adrenal cortex, especially in patients who are quite ill or during periods of infection. For patients in an Addisonian crisis, the treatment of choice appears to be large amounts of adrenal cortical extract combined with solution of sodium chloride and sodium citrate injected intravenously. Adrenal cortical extract manifests both the electrolyte and the carbohydrate metabolic activities of the gland, and thus more nearly approaches complete replacement therapy than any single crystalline cortical hormone at present commercially available.

Quinine in Myotonia Congenita. Myotonia congenita or Thomsen's disease, a rare myopathy of unknown origin, is the pharmacological antithesis of myasthenia gravis. Recently, quinine has been found to be effective in the symptomatic treatment of the tonic spasm of skeletal muscles characteristic of the syndrome. The myotonic symptoms are quickly and sometimes entirely relieved, and the abnormal electrical reactions return to normal. The basis of the action of quinine is its ability to abolish the abnormal sensitivity of the myotonic muscle to mechanical stimulation. Therapy is not curative and benefit is obtained only as long as the alkaloid is given. It is of interest that quinine also is effective in obliterating the muscular rigidity in goats suffering from a form of congenital myotonia similar to that occurring in humans.

Papaverine in Arterial Embolism. Papaverine, the chief member of the benzylisoquinoline group of opium alkaloids, has long been known in therapeutics, but only within recent years has it become firmly established as a valid and useful vasodilator in the emergency treatment of peripheral or pulmonary arterial embolism. For this purpose, it is injected intravenously in generous doses, and is often saving of life as well as limb.

Heparin in Prevention and Therapy of Thrombosis and Embolism, in Blood Vessel Surgery, etc. Within recent years, heparin has been sufficiently purified and reduced in price to the extent that it is now available for clinical use. It has been found of value in the therapy of a wide variety of medical and surgical conditions and procedures, including surgery of blood vessels, blood transfusion, prevention and treatment of thrombosis and embolism, thrombophlebitis, etc. The chemistry and mechanism of action of heparin have been considerably elucidated of

TABLE II

PROMISING NEWER THERAPIES REQUIRING FURTHER STUDY BEFORE BEING GENERALLY EMPLOYED

Newer digitalis glycosides	Sobisminol (orally in syphilis)	Metopon (morphine substitute)
Benzedrine (in epilepsy, in parkinsonism)	Rotenone (in scabies, in chigger-mite dermatitis)	Gramicidin (in bacterial infections)
Picrotoxin (in barbiturate poisoning)	Benzyl benzoate (in scabies)	Penicillin (in bacterial infections)
Curare and erythroidine (in certain neuromuscular syndromes)	Phenothiazine (in enterobiasis)	Synthetic estrogens (stilbestrol)
Organic mercurial diuretics (by mouth)	Gentian violet (in enterobiasis, strongyloidiasis)	Progesterone (in threatened or habitual abortion, functional bleeding, dysmenorrhea, afterpains, etc.)
Short-term massive arsenotherapy (in early syphilis)	Atabrine (in giardiasis)	
	Plasma protein precursors (intravenously)	

late, and the drug has at last become a valuable addition to the physician's armamentarium.

GROUP II

In Group II are listed those recent advances in drug therapy which are very promising, but which require further clinical study before being generally employed in daily practice (Table II). Likewise included are those recent contributions which, though purely in the experimental stage of investigation, show every promise of eventually proving to be therapeutically useful.

Newer Digitalis Glycosides. In recent months, the "native" glycosides of the lanata species of digitalis have received considerable attention, particularly in comparison with digitalis purpurea, the official U.S.P. source of digitalis. The three native glycosides of digitalis lanata are known as lanatosides A, B and C. When all three are employed, their combination provides an acceptable digitalis preparation for oral use, but this does not mean that such a preparation possesses any compelling advantages. Being water-soluble, lanatoside C has been employed for intravenous administration, but this route is warranted, as a rule, only when digitalis medication must be given quickly, that is, when minutes rather than hours determine the difference between life and

death. If the clinical findings obtained with lanatoside C are confirmed by further study, it is likely that this drug may then be added to the list of older and better known water-soluble, crystalline cardiac glycosides serviceable for parenteral administration, such as ouabain and strophanthin.

One can not help but take this opportunity critically to examine the advantages claimed for crystalline digitalis glycosides as compared to official galenical preparations, such as the powdered leaf and tincture. These claims include accuracy of dosage, a wider margin of safety (of lanatoside C, in particular), and the stability of purified crystalline preparations. While it must be admitted that the U.S.P. bioassay of digitalis allows much to be desired, no serious difficulty need arise therefrom in daily practice. In the last analysis, any *particular* product, galenical or purified, must be assayed on *each* patient, and individuals may vary considerably. The claim concerning the higher margin of safety of lanatoside C is especially misleading. All cardiac glycosides have the same basic action on the failing heart, namely, to increase the tone and force of contraction of the heart muscle. No good evidence exists that the toxic properties of digitalis-like drugs can be dissociated from their therapeutic actions. Therefore it remains to be proven that there are clinically significant variations in margins of safety between galenical digitalis preparations and purified glycosides. The toxic actions of all digitalis-like drugs are merely extensions of their therapeutic effects. Their potency or toxicity depends not on the degree of purification before being wrapped in the package, but on the amount of drug swallowed by the patient. The claim concerning stability is also misleading because all reliable studies show that galenical preparations of digitalis keep for many years without significant loss of potency. Finally, cost is an important factor, since most patients must take digitalis for life. By and large, the purified glycosides are much more expensive than U.S.P. digitalis leaf. Furthermore, even the lanatosides must undergo further chemical changes in the body before their active principles are released, and the patient's intestinal juices can release these principles from crude digitalis leaf as effectively as can the pharmaceutical chemist, and also much more cheaply.

For all these reasons, it is the opinion of the reviewer that in the overwhelming majority of patients with heart failure, one will find that U.S.P. powdered digitalis leaf is easy to administer, is readily absorbed

when given by mouth, is effective in its action on the myocardium, possesses an adequate margin of safety, is stable in potency, and that cumulation and elimination occur in the body at rates allowing complete digitalization at varying speeds and satisfactory maintenance of desired therapeutic effects for long periods of time. The burden of proof that any digitalis substitute or purified fraction is more valuable than U.S.P. digitalis still rests on those making such a claim. The general practitioner will do well for the present to select his therapeutic agents from U.S.P. preparations, and to leave the final evaluation of purified glycosides to the experimental investigator. Both he and his patients stand to gain thereby.

Benzedrine as an Adjuvant in Epilepsy and Parkinsonism. Benzedrine, one of the newer members of the epinephrine family, has recently been put to two promising uses, which, if substantiated by further clinical experience, will indeed represent definite therapeutic advances. Benzedrine differs from some of its immediate chemical relatives by having a powerful stimulant action on the central nervous system. This action is especially useful, for example, in the treatment of narcolepsy, and for the therapy of poisoning by central nervous system depressant drugs. Of particular interest at the moment is the fact that benzedrine may prove to be a valuable adjuvant to phenobarbital in the symptomatic treatment of epilepsy. Certain patients require large amounts of phenobarbital to control seizures. These large doses are likely to cause sufficient dizziness, ataxia and drowsiness to prevent the employment of phenobarbital. The concomitant use of benzedrine dissipates the untoward effects, and allows doses of phenobarbital to be employed which otherwise would be impossible. Apparently benzedrine used in this manner has no untoward effect on the character or incidence of the seizures.

Benzedrine is also a valuable adjuvant to belladonna alkaloids in the symptomatic therapy of postencephalitic parkinsonism. The mechanism of this action is not fully understood. In conjunction with atropine, scopolamine, stramonium or mixtures of belladonna alkaloids, benzedrine may allow a better sleep cycle, increased energy, subjective improvement in muscle strength and rigidity, and relief from oculogyric crises. Indeed, benzedrine appears to be almost a specific for oculogyric crises, the attacks being reduced in number and severity, or entirely disappearing. Best results are obtained when the disease is postencephalitic

rather than arteriosclerotic in origin, and when organic defects and personality changes are minimal.

Picrotoxin in Barbiturate Poisoning. Picrotoxin is another central nervous system stimulant. Until recent times, it was largely a laboratory curiosity. It is capable of lessening the degree of depression and of stimulating respiration in patients poisoned by anesthetic agents, especially barbiturates, against which it appears to be an effective pharmacological antagonist. The ultimate status of picrotoxin in comparison with better known analeptic agents, such as caffeine, strychnine, ephedrine, carbon dioxide and metrazol, remains to be determined. Like strychnine, it must not be employed in the treatment of morphine poisoning.

Curariform Drugs in Certain Neuromuscular Syndromes. Passing from central nervous system stimulants to skeletal muscular depressants, some mention may be made of curare, which in recent months has received considerable attention in the lay as well as the medical press. Curare and certain other alkaloids such as erythroidine, are capable of depressing neuromuscular junctions of skeletal muscles so that the response to nerve impulses is diminished or abolished. Older sporadic attempts to use curare clinically met with little success, due chiefly to difficulty in obtaining purified and standardized preparations. Lately, however, curare has been employed for the prevention of traumatic fractures incident to the metrazol therapy of schizophrenia. This has reawakened interest in the use of curare for other syndromes, and some measure of success has been obtained in patients with spastic paralysis, dystonia musculorum deformans, and torticollis. It is to be hoped that the active investigations now under way in a number of laboratories and clinics will provide curare-like preparations suitable for clinical use, and possessing a selective action on abnormally functioning muscles, as well as a wide margin of safety regarding respiratory and cardiovascular depression.

Oral Administration of Mercurial Diuretics. The successful use of organic mercurial diuretics by the rectal route allowed the hope that it would eventually be possible to give these valuable agents by mouth in patients with edema or ascites due to heart failure or cirrhosis of the liver. That hope stands on the threshold of realization and within the last year successful results have been obtained with a preparation of salyrgan combined with theophylline. Satisfactory diuresis results in approximately 70 per cent of patients. Although this figure is below

the 95 per cent success achieved by the intravenous route, it is higher than the 60 per cent obtainable by the use of mercurin suppositories. Untoward gastrointestinal symptoms such as epigastric discomfort and diarrhea are mild and infrequent. In patients who are not acutely ill and do not require immediate and drastic diuresis, the oral preparation may well prove to be the agent of choice and to have a definite advantage over the rectal route. At present, the drug is released only for investigational purposes, but if the success to date continues to be confirmed, it may soon be routine to administer mercurial diuretics by mouth. In employing either the oral or rectal route, the major contraindication to the use of mercury must still be rigidly observed, namely, that mercury is not to be employed if renal function is noticeably impaired. This holds true regardless of the cause of the edema.

Short-Term Massive Arsenotherapy of Early Syphilis. Being residents of the New York area, most of you undoubtedly are fully aware of the highly important work being done with the massive short-term arsenotherapy of early syphilis. This therapy holds great promise, and the public health and economic advantages are evident to all. Immediate clinical and serologic results are quite favorable, but several more years of intensive study will be required before the late clinical results can be determined and compared with those obtainable by the accepted routine of prolonged continuous therapy, as sponsored by the Cooperative Clinical Group. Much remains to be learned concerning optimal dosage, the arsenicals of choice, the duration of therapy, and the exact incidence of toxic reactions. It must be emphasized that the treatment is still relatively new and should be conducted mainly in those medical centers where adequate facilities for careful study are available. Only harm can come from promiscuous use of the method. It should be confined to patients with *early syphilis* and is strictly a hospital procedure. Deviations from the outline of treatment as described by the originators of the continuous intravenous drip arsenotherapy should be undertaken only by experts.

Sobisminol in the Oral Therapy of Syphilis. The status of bismuth as an adjuvant in the therapy of both early and late syphilis is well known. To the patient, however, an unpleasant feature of conventional treatment with bismuth is the necessity of intramuscular injection of the metal. Lately, it has been demonstrated that certain salts of bismuth in special solvents are adequately absorbed after oral administration

and exert chemotherapeutic effects in the tissues. Although this work is still in the investigational stage, the reports to date are promising. The preparation accepted by the Council on Pharmacy and Chemistry for oral use is *sobisminol mass*. Until more is learned concerning the action of sobisminol mass in syphilis, its employment should probably be restricted to patients unable to receive intramuscular therapy, and to supplant treatment by that route in patients compelled for a time to be out of contact with their physicians. Special limitations and dangers accompany the use of bismuth by the oral route, and these should be understood before employing it.

Rotenone as a Contact Insecticide. Rotenone is a drug recently introduced in clinical therapeutics after a successful career as a contact insecticide in agriculture and veterinary medicine. It has received much prominence in magazine articles and its collection, importation and use in the United States represent a growing and important industry. Obtained from derris root and at present from the South American cubé root, rotenone is a highly complex organic compound which is very toxic for insect pests but relatively harmless to warm-blooded animals. Its chief value in therapeutics is for scabies and for chigger-mite dermatitis. It is applied in the form of a one or two per cent lotion. Rotenone treatment is apparently effective and has the definite advantages over the usual scabeticides in not being odorous or messy, or causing staining or skin irritation.

Benzyl Benzoate as a Scabeticide. While on the subject of scabeticides, a word should be said about benzyl benzoate, a drug which had a short clinical trial about 15 years ago as an antispasmodic, a property which it fails to exhibit clinically. Benzyl benzoate now turns out to be an efficient scabeticide, and has been shown by the British to be effective after a *single* application. It has been found especially useful when people are living under air raid conditions and the danger of infection is great. Benzyl benzoate is applied as a lotion, which can be made with equal parts of the drug, soft soap, and alcohol.

Phenothiazine in Enterobiasis. Phenothiazine is another contact insecticide employed in agriculture as a lead and arsenic substitute with low toxicity for mammals. It was quickly found to be an excellent vermifuge for cattle, swine, sheep and horses. The urine of animals given phenothiazine was observed to turn red on exposure and not to putrefy. Investigation showed that phenothiazine — the mother substance of

methylene blue and certain other dyes—is excreted in the urine and eventually oxidized to thionol, a red antiseptic dye, especially if the urine is acid. This led to the clinical trial of phenothiazine as a urinary antiseptic. Although the drug showed considerable promise, mandelic acid was already firmly entrenched as a urinary antiseptic, and the sulfonamides were rapidly rising to first place. Not to be deterred, phenothiazine moved on to new fields and has within the last year been shown to be a very effective agent in the treatment of pinworms. Although enterobiasis hitherto has been particularly difficult to treat in children, it appears that a single five-day course of phenothiazine will cure 90 per cent of cases, and untoward symptoms are not experienced.

Gentian Violet as an Anthelmintic. Gentian violet, an antiseptic dye, is not a new drug but recently it has been put to new uses. It too has been found quite effective in the treatment of pinworm infestation. Like phenothiazine, it cures 90 per cent of cases after a single 10-day course of treatment. Unlike phenothiazine, however, gentian violet causes mild untoward gastrointestinal effects in a considerable number of persons receiving it. Gentian violet has also been found of value in the treatment of strongyloidiasis.

Atabrine in Giardiasis. Before leaving the subject of human parasitic infestations, mention should be made of the fact that atabrine, an effective synthetic antimalarial drug, has within the last year been established as a curative agent for giardial infestation in man. The dose employed is similar to that used in malaria, and cure is effected in nearly 100 per cent of patients. It is now possible to determine whether giardial infestation produces symptoms, because the organism is usually considered to be nonpathogenic for humans. Nevertheless, a large number of patients harboring the parasite complain of diarrhea, abdominal pain, asthenia and irritability. Evidence exists that a significant number of such patients may be freed of their symptoms by treatment with atabrine. Further work may indeed establish that the flagellate is mildly pathogenic. In any event, atabrine would appear to be a specific cure.

Intravenous Administration of Plasma and Tissue Protein Precursors. An extremely important field of research which may soon have direct clinical applicability concerns the parenteral administration of precursors of tissue and plasma proteins. The possibility of administering protein or its precursors by routes other than the oral has long engaged the imagination of medical investigators. Such therapy would prove

valuable in the treatment of a variety of conditions including hypoproteinemia, certain types of malnutrition, and dysfunctions of the enteric tract due to disease or surgery, characterized by inability to take sufficient protein by mouth. It has already been possible to inject amino-acid mixtures or protein digests intravenously in humans without appreciable toxic effects. Further advance in this important field awaits development of the proper types of commercial preparations—minimal criteria being lack of toxicity, reasonable price, and ability to meet the nitrogen requirements of the body. It is perhaps well to emphasize that this type of therapy is not suitable for shock, in which condition better and more rapidly acting therapeutic agents are available.

Synthetic Morphine Substitutes. The general practitioner is probably unaware that from 1929 to 1941, an extensive coöperative research program was in progress to study morphine, its derivatives, and substitutes, under the joint auspices of the National Research Council, The Narcotic Bureau of the United States Public Health Service, and the Universities of Virginia and Michigan. Many valuable contributions emerged from this extensive investigation. Of the many substitutes for morphine which were synthesized and studied, the one most promising is known as "metopon." Chemically, it is a methyl derivative of dilaudid. It appears to have definite advantages over morphine in that respiratory depression and emetic properties are less noticeable, and analgesic potency is more prominent than euphoria or narcosis. It also seems that metopon may have less liability for producing addiction. In other words, metopon offers greater analgesic power with less risk of addiction and with fewer untoward side-actions. Further clinical experience, however, is required to substantiate these findings. At present the drug is available only for investigational purposes.

Gramicidin in Bacterial Infections. The discovery of sulfonamides undoubtedly provided a sharp impetus to chemotherapeutic research in general, and particularly with regard to antibacterial agents. The good earth which yields our sustenance contains a wealth of important bacteria capable of performing many remarkable biochemical reactions. In 1939, from an aerobic sporulating soil bacillus, Dubos and associates isolated a bactericidal crystalline principle which selectively kills Gram-positive cocci, and which was therefore named gramicidin. Gramicidin is a crystalline substance, soluble in alcohol and acetone but not in water, and containing a number of amino-acids combined to form a

polypeptide. In the test tube, as little as 0.005 mgm. of gramicidin kills one billion pneumococci or group A hemolytic streptococci. The meningococcus and gonococcus are moderately affected, but Gram-negative bacilli are not susceptible. In mice, for example, a single intraperitoneal injection of 0.001 mgm. of the drug protects against 10,000 minimal lethal doses of pneumococci or streptococci, and larger doses cure well-established infections. Preparations of gramicidin at present available are not only water-insoluble but are also hemolytic. This restricts their clinical use to local application to the body surface and to irrigation of closed cavities. However, there is good reason to believe that water-soluble and non-hemolytic fractions of the drug may soon be available. Gramicidin has shown considerable promise in preliminary clinical trials in a variety of infections caused by Gram-positive cocci. Among the conditions successfully treated are the following: infected stasis ulcers, acute maxillary sinusitis, eczematoid dermatitis, wound infections, persistent cystitis, and pneumococcal empyema. No evidence of systemic toxicity has been reported as yet, tissues are apparently undamaged and healing of wounds is accelerated. Many problems concerning gramicidin are being actively studied and its eventual status, especially in comparison with local sulfonamide therapy, remains to be determined. The outlook, however, is very promising. At present, gramicidin is available only for investigational purposes.

Penicillin in Bacterial Infections. Another potent bactericidal agent obtained from cultures of microbial cells is penicillin, discovered in 1929 by Fleming, but developed to the point of clinical applicability only within the last year. Penicillin is so named because it is produced by a mould, probably *Penicillium notatum*, a first cousin to the mould responsible for the ripening of Camembert cheese. It is extracted from the culture medium, dried by the lyophilic method, and consists of a yellow, water-soluble powder, the chemical composition of which is not yet determined. Penicillin is active against a variety of microörganisms in dilutions of one to a million or more, including the streptococcus, staphylococcus, gonococcus, meningococcus, and anaerobes of the gas gangrene group. For example, in the test tube, 0.001 mgm. in one cubic centimeter of culture medium will inhibit the growth of 2,500,000 hemolytic streptococci. Most of the Gram-negative bacilli, however, are unaffected except by high concentrations. Experimentally, animals are protected by penicillin against numerous bacterial infections, and

mice can be prevented from succumbing to 100,000,000 lethal doses of streptococci. Penicillin differs from sulfonamide drugs in three important ways: First, it is more potent. Secondly, it completely inhibits bacterial growth even when the cultures are heavily inoculated, and this is of great importance in the therapy of heavily infected wounds. Lastly, penicillin is not inhibited by tissue autolysates, an advantage in the therapy of suppurating wounds. Being water-soluble, it can be administered to patients by a variety of routes, including the intravenous. Although clinical studies are as yet meager, those conducted by the group in Oxford, England are particularly encouraging. The drug has been employed successfully in patients with a variety of bacterial infections, including osteomyelitis, urinary tract infections, large carbuncles, infectious conjunctivitis, etc. It has proved valuable in cases which failed to respond to surgery or sulfonamides. Toxic effects have not been observed. At present, the chief handicap is the inadequate supply of the drug. The available evidence suggests that penicillin is an effective and potent chemotherapeutic agent of low toxicity, but its ultimate status in relation to gramicidin and sulfonamides remains to be determined.

Synthetic Estrogens (Diethylstilbestrol). In recent years, much experimental and clinical work has been done with synthetic estrogens. These differ from naturally occurring estrogens in that they are derived from a chemical known as diphenylethylene or stilbene. The most active member has therefore been named stilbestrol (diethylstilbestrol) because of its high estrogenic potency. The actions of diethylstilbestrol are almost identical with those of the naturally occurring estrogens, but the compound is many times more potent than estrone when administered orally, and from two to four times more active when given parenterally. However, after parenteral administration, it is less active than estradiol. The therapeutic indications for diethylstilbestrol are the same as for the naturally occurring estrogens, and the drug has been successfully employed in the treatment of many of the conditions requiring estrogenic therapy, such as menopausal symptoms, senile vaginitis, gonococcal vulvovaginitis, etc. The two outstanding advantages of diethylstilbestrol are first, that it can be given conveniently by mouth, and secondly, that it is much cheaper than other estrogens. However, there is some evidence that its use results in a fairly high incidence of mild toxic reactions, especially nausea and vomiting. Although not all

investigators have noted a significant incidence of untoward reactions and while it seems likely that these are mainly due to overdosage, nevertheless more information must be obtained to demonstrate that diethylstilbestrol is relatively non-toxic, and this factor should be weighed against those of cost and ease of administration in determining the choice of estrogenic preparation.

Progesterone Therapy in Threatened or Habitual Abortion, Functional Bleeding, Dysmenorrhea, etc. Although the active principle of the corpus luteum was isolated and chemically identified in 1934, the synthetic commercial preparation has been available for general use only within recent years. Sufficient clinical data have now accumulated to indicate the worth of progesterone therapy, but it must be emphasized that such therapy is relatively new and still in the stage of clinical experimentation. Progesterone has been employed successfully in threatened abortion. However, threatened abortion may be due to a defective embryo, and the administration of progesterone may then defeat nature's purpose in expelling the abnormal embryo. The drug has also been used in certain cases of habitual abortion. The mechanism of action of progesterone in maintaining pregnancy is apparently the suppression of uterine motility and, in the earlier stages of gestation, the maintenance of a proper type of endometrium to insure an adequate circulation to the fetus. The hormone may also logically be tried in certain cases of continuous functional uterine bleeding. The cause of the bleeding may be due either to endometrial hyperplasia associated with a progesterone deficiency or to hyperestrinism. In either case, progesterone therapy may be beneficial, but this should not obscure the fact that such a syndrome is based on an ovarian dysfunction. The cause of the dysfunction, often hypothyroidism, should be determined if possible. Reports of success with progesterone in some cases of dysmenorrhea are probably based on the fact that the hormone diminishes uterine motility. The same mechanism is concerned in the use of progesterone for afterpains following parturition.

Group III

In Group III are included those newer therapies which, in the opinion of the reviewer, are of questionable value and require much further investigation to delineate their proper status (Table III). Because of the controversial nature of the subject matter and the limitation of

TABLE III

RECENT THERAPIES OF QUESTIONABLE VALUE

Histamine (in allergic diseases)
Adrenal cortical hormones (in therapy and prevention of shock)
Renal anti-pressor extracts and tyrosinase (in essential hypertension)
Convulsive or shock therapy of schizophrenia (metrazol, insulin, nitrogen, etc.)

time, only the briefest mention can be made of the topics in this category.

Histamine Therapy in Allergic Disorders. The indiscriminate use of histamine in a heterogeneous group of allergic diseases is certain to lead to disappointing results and to prevent a clear appraisal of the true worth of histamine desensitization therapy. While there is some evidence that histamine may be the causative agent of anaphylactoid symptoms produced by cold, its role in the etiology of other than physical forms of allergy is far from clear. The use of the amine in desensitization therapy must be considered for the present to be a procedure the value of which is far from established.

Adrenal Cortical Hormones in the Prevention and Treatment of Shock. The clinical use of desoxycorticosterone or other adrenal cortical hormones for the prophylaxis and treatment of shock is still a questionable procedure. Undoubtedly the employment of the hormone with large amounts of sodium chloride solution serves to increase the circulating blood volume by retention of salt and fluid. It is not clear, however, how such therapy could prevent the *onset* of shock, considering the pathological physiology of the syndrome. Also, there is real danger of overtaxing the circulation. The objective in treating shock is to increase the blood volume. Desoxycorticosterone does this by a renal mechanism. Shock is usually associated with anuria and the problem is not the loss of circulating fluid through the kidney but rather through widely dilated or injured capillaries. Until it has been more definitely shown that the adrenal cortical hormones influence the distribution of body fluids by affecting the permeability of capillaries, their use in shock must be viewed with a good measure of skepticism. Certainly, the clinical evidence is as yet too meager to warrant any definite conclusions as to the ultimate value of such therapy. Furthermore, a similar view must be adopted toward any other disease or symptom in which

the hormone is alleged to bring relief by a local corrective action on an increased permeability of capillaries.

Renal Extracts and Tyrosinase in the Therapy of Essential Hypertension. The technic of renal ischemia devised by Goldblatt for producing experimental hypertension in animals initiated an extremely important field of research which has profound implications for pathology and medicine. Not the least of these is the necessity for carefully reexamining all patients diagnosed as having essential hypertension with a view of ascertaining whether occult renal pathology is possibly responsible for the high blood pressure. Several investigators have attempted to isolate the vasopressor substance produced by renal ischemia, and extracts of kidney with antipressor properties have been prepared which are capable of preventing or reducing experimental hypertension in animals. Likewise, the enzyme tyrosinase, which is found in fruits and vegetables and especially in mushrooms, and which is capable of inactivating pressor amines such as tyramine and epinephrine, has been found capable of inactivating renin and angiotonin. This enzyme has also been found capable of lowering the blood pressure in experimentally produced hypertension in rats and dogs. Both tyrosinase and antipressor renal extracts of various sorts have been tried clinically and have been shown to be capable of lowering blood pressure in patients with essential hypertension. Despite the reported manometric success, this field of clinical investigation is altogether too new for one even to hazard a guess at the results which may ultimately develop. The capable workers engaged in this research would be the last to object to seeing their attempts at therapy of essential hypertension classified as questionable until much more clinical evidence is available.

Convulsive or Shock Therapy of Schizophrenia. With regard to the convulsive or shock therapy of schizophrenia, whether induced by drugs such as metrazol or insulin, or by other means such as nitrogen, it is the opinion of the reviewer, from an examination of the available evidence, that such treatment has questionable and certainly limited value, and is not without serious danger. Clearly, the procedure should be restricted to institutions where the staff is adequately trained in this highly specialized technique. The mechanism of action is not clear, and whether the alleged favorable results are due to temporarily reduced cerebral oxidations or to actual cortical damage is not known. So many "cures" of schizophrenia have been endorsed enthusiastically only to be

TABLE IV

RECENT THERAPIES OF LITTLE OR NO VALUE

Pyridoxine (in parkinsonism, amyotrophic lateral sclerosis, muscular dystrophies)
Alpha-tocopherol (in amyotrophic lateral sclerosis, muscular dystrophies, habitual abortion)
Testosterone (in "male climacteric," prostatic hypertrophy, etc.)
Histaminase (in allergic diseases)
Potassium salts (in allergic diseases)
Bulgarian belladonna (in parkinsonism)

discarded after long-term study that one can hardly be criticized for adopting a cautious view with regard to convulsive or shock therapy. This cautious view necessitates that such therapy be classified for the present as questionable and requiring much further study before its ultimate worth can be ascertained.

GROUP IV

In Group IV are placed those newer drug therapies which, in the opinion of the reviewer, are either extremely questionable in value, or irrational and destined for eventual discard (Table IV).

Pyridoxine in the Therapy of Parkinsonism, Amyotrophic Lateral Sclerosis and Muscular Dystrophies. Pyridoxine, or vitamin B_6, is a recently discovered component of the vitamin B complex. Although essential in animal nutrition, its significance in human nutrition is not yet known. Therefore, pyridoxine has no clear-cut therapeutic indications, and until such time as specific deficiencies are attributable to its lack it cannot be considered an indispensable drug. This does not mean that the active research now being conducted will not soon yield results translatable into daily practice; but, it does explain why disease entities not specifically due to a lack of pyridoxine cannot reasonably be expected to respond to pyridoxine therapy. Thus, the early sanguine reports of success with pyridoxine in treating such varied syndromes as parkinsonism, amyotrophic lateral sclerosis, and muscular dystrophies have not been confirmed by carefully controlled clinical experiments. One may safely venture the prediction that when pyridoxine is ultimately established as a valid therapeutic agent, it will be for treatment of diseases or symptoms specifically due to a lack of the vitamin.

Alpha-Tocopherol in the Therapy of Amyotrophic Lateral Scle-

rosis, Muscular Dystrophies, and Habitual Abortion. Alpha-tocopherol, or vitamin E, is not a new vitamin, but it has only recently been synthesized. Although it is apparently necessary in the nutrition of certain but not all species of animals, its significance in human nutrition is unknown. Because growth, normal pregnancy and prevention of muscular dystrophies in rats require alpha-tocopherol in the diet, the drug was quickly tried in humans with disturbances only superficially resembling the deficiency states observed in animals, and with results that one might easily anticipate, namely, not very encouraging. Thus the early enthusiastic reports concerning the use of alpha-tocopherol in amyotrophic lateral sclerosis, pseudo-hypertrophic muscular dystrophy, and habitual abortion were destined to be challenged and denied by later more carefully controlled clinical experiments and observations. As in the case of pyridoxine, indeed, as in the case of all vitamin principles, one may safely predict that when the clear-cut indications for alpha-tocopherol are finally disclosed, they will certainly relate to deficiency states proven to be specifically due to a lack of the vitamin.

Testosterone in the Therapy of "Male Climacteric," Prostatic Hypertrophy, etc. Testosterone has been employed clinically only within recent years. Although experience with it is therefore limited, evidence is available concerning its unquestionable value in both prepuberal and postpuberal castrates. Indeed this use appears to be the main field of valid therapy with testosterone. Unfortunately, older concepts concerning the male sex hormones are influencing modern therapy, and one can detect a trend toward emphasis on the ability of androgens to restore sexual activity. Advertising brochures thus recommend their use in such vaguely defined conditions as the "male climacteric" and "atonicity." Such exploitation can do much harm. Also, on rather incomplete evidence, testosterone has been employed for prostatic hypertrophy, but there is little reason to believe that androgen therapy can cause the involution of an existing hypertrophy. Indeed, there is always the possibility that it may cause a still greater enlargement of the gland. Furthermore, testosterone has been employed for relief of a wide variety of conditions, including dysmenorrhea, menopausal states, peripheral vascular disease, painful breasts, menorrhagias, and for interruption of lactation. Much more evidence is required before one can say whether such therapy is rational or safe. It is indeed unfortunate that as soon as an endocrine principle or vitamin is isolated in pure form, synthe-

sized and placed in ampules, it is used indiscriminately in a variety of unrelated diseases, and an avalanche of uncritical case reports is soon loosed upon the medical profession. It often takes years to unearth the truth from this avalanche. A clear understanding of the basic physiology involved should greatly assist one properly to select those clinical conditions in which there is an adequate rationale for specific hormone therapy.

Histaminase in the Therapy of Allergic Disorders. Histaminase is an enzyme which, under special test-tube conditions, can inactivate histamine. It has been widely employed in a large heterogeneous group of allergic conditions. As with all new therapies, some enthusiastic initial reports are bound to appear, but slowly the long-term and more deliberate studies serve to nullify or reverse the original over-enthusiastic appraisal. In the opinion of the reviewer, those most qualified to pass judgment on histaminase therapy have adequately proven not only its unsound theoretical rationale, but also its clinical inefficiency. The physiological background concerning the enzyme and the role of histamine in allergy are both so poorly understood, it is little wonder that the clinical use of the enzyme is disappointing. To those who claim that they have occasionally obtained excellent results with histaminase, one can only reply by reminding them of the vagaries and perversity of biological subject matter.

Potassium Salts in the Therapy of Allergic Disorders. What has been said with respect to histaminase in the therapy of allergic conditions holds true for potassium salts even to a greater extent, if that is possible. While salts of potassium are useful in promoting diuresis, in preventing or curing attacks in patients with familial periodic paralysis, and in the diagnosis of Addison's disease, it remains to be demonstrated that they are of any benefit whatsoever in the treatment of diseases of allergy. The theoretical basis for the employment of potassium salts is nebulous and the extravagant claims made for such therapy are fully disproved by the results of carefully controlled clinical studies. Indeed, how can one expect to obtain dramatic relief from allergic symptoms by the administration of a daily dose of potassium which represents but a small fraction of the normal daily dietary intake of this ubiquitously distributed cation?

Bulgarian Belladonna in the Treatment of Parkinsonism. As you probably know, Bulgarian belladonna root has recently enjoyed some

popularity in the symptomatic treatment of patients with parkinsonism, and exaggerated claims have been made for its virtues. One can summarize the best information available on this question by stating flatly that Bulgarian belladonna root has no special advantages over belladonna root grown in the United States. However, as a result of the unfounded claims made for Bulgarian belladonna root, there has resulted a re-examination of the use of alkaloidal mixtures in parkinsonism. Studies now in progress may eventually show that U.S.P. Belladonna Root is superior to official belladonna leaf, at least in some patients. It also may eventually prove to be true that white wine extracts occasionally give better results than tinctures. Finally, there is some evidence that certain individuals respond more satisfactorily to mixtures of purified alkaloids than to any single alkaloid employed alone. These points, however, remain to be determined. What is certain is the fact that one may safely continue to patronize home-grown belladonna.

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A NOTE ON WAR PSYCHIATRY*

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At the time of our joining our allies in the first World War, American Psychiatry had the advantage of scrutinizing the experiences of the other combatant nations on both sides of the struggle with respect to the psychiatric issues involved. Our attention was challenged by two important facts which were reflected in the published accounts of the medical authorities of the nations at war: First, the substantially greater prevalence of psychiatric casualties among soldiers than among the civilian population, and second, the emergence of new and hitherto unobserved disorders of function which were in a general way referable to the nervous system.

With respect to the first observation, namely, the markedly increased incidence of psychiatric casualties among troops, it was observed that not only in actual war but even during peaceful mobilization, such as that of our army along the Mexican border in 1916, there was a higher rate of mental disease among soldiers than in civil life. The discharge rate for mental diseases in the United States Army in 1916 was three times the admission rate for these disorders in the adult male population of the State of New York, one-tenth of all discharges for disability being for mental diseases, mental deficiency, epilepsy and the neuroses.

It was largely through the efforts of the late Thomas W. Salmon that the significance of these observations was brought to the attention of the medical authorities of the War Department, which up to then had shown relatively little concern in psychiatric issues. As a result largely of Salmon's efforts, the coöperation of the Army Medical authorities was gained for putting into practice the recommendations outlined by a group of psychiatrists and neurologists under Salmon's leadership. It was my privilege to participate in the early deliberations on these matters and I wish to take the opportunity here of attesting to the rare wisdom, courage and high qualities of leadership which Salmon displayed during

* Read at the annual meeting of the New York Society for Psychotherapy and Psychopathology at The New York Academy of Medicine.

these deliberations. It would serve no particular purpose to give a detailed account here of the clinical and administrative techniques which were finally adopted, although I shall go into greater detail later on with respect to the clinical aspects of the subject.

At the time of the creation of the Division of Neurology and Psychiatry in the Surgeon General's office, about fifty neuropsychiatric officers had been commissioned. Five months later there were two hundred and thirty-five, and at the time the armistice was signed there were 430 officers in this country and 263 overseas, a total of 693. I mention these figures in order to indicate the drain which the requirements of the Selective Service Administration will mean to civilian psychiatry. These officers were assigned in a general way to two types of duty: First, the routine neuropsychiatric examination of recruits, and second, clinical and administrative service in base and other military hospitals.

It was impossible to determine with absolute accuracy how many men were examined by the neuropsychiatrists in this country, but the figure finally adopted for statistical considerations was 3,500,000. Of this number there was a total of 69,394 psychiatric diagnoses, and of these 533 referred to officers and 587 to candidates for commission.

These psychiatric diagnoses comprised the following entities: 31.5 per cent mental deficiency; 16.5 per cent psychoneuroses; 11.4 per cent psychoses; 10 per cent nervous diseases and injuries; 9.2 per cent epilepsy; 8.9 per cent constitutional psychopathic states; 6.9 per cent endocrinopathies; 2.9 per cent drug addiction; 2.7 per cent alcoholism.

Thus 20 out of every 1000 examined had some form of mental or nervous disease or defect.

According to the British official history of the Great War, the psychiatric problem in the British Expeditionary Forces did not become acute until July 1916, when several thousand patients were rapidly passed out of the Somme battle zone. An analysis of 1,043,653 British casualties revealed that neuroses formed 34 per 1000 casualties. On occasions neuroses made up 40 per cent of the casualties evacuated home. In 1918 out of a total 160,000 pensioners, 32,000, or 20 per cent, were receiving pensions for functional nervous and mental disease, while in 1921 this figure had risen to 65,000. Of the 180,496 casualties which occurred in the Canadian Expeditionary Force, 24 per 1000 were included in the category of nervous and mental disease.

According to various authors, the incidence of psychiatric casualties

was relatively greater in fresh troops arriving in the front line; in battle-tested troops after prolonged trench life without a break; in men over 40, especially married men, and in rapidly trained volunteers as compared with the regular army. The incidence rose considerably after severe military operations, actively advancing troops were less liable to breakdown than inactive or retreating troops, technicians working at the front under extreme hazard, infantry and machine gunners, engineers, artillery and tank corps ranked high on the list.

It is interesting to compare the above ratios of casualties in the B. E. F. and C. E. F., 34 to 40 per thousand in the former and 24 per 1000 in the latter with the ratio of casualties in the A. E. F., where during the period between April 1917 and December 1919 it was 9.5 per 1000. One reason for this markedly lower incidence of psychiatric casualties among the A. E. F. that is frequently given, especially by foreign authorities, is the comparatively short period of active service that our forces had abroad. While this factor cannot be ignored, I would like to stress especially in this connection two other factors which account for this important difference in the ratio of casualties. The first is the really competent job which the neuropsychiatrists did in weeding out the incompetents on this side of the ocean. It is significant in this connection that 27,836 cases or 40.1 per cent of the total of 69,394 were detected and certified as unfit in the course of the routine neuropsychiatric examinations. Other sources of spotting the unfit were as follows: 31.6 per cent came to light as result of psychiatric consultations requested by other medical officers; 23.6 per cent were referred by commanding officers, non-medical. In connection with this truly significant item, namely that 16,336 cases of psychiatric abnormalities were detected by line officers, I would like to stress the great importance of a deliberate and well organized technique for educating non-commissioned as well as commissioned officers to observe and recognize abnormalities of conduct which was carried out by the American neuropsychiatrists as part of their routine duties. This is one feature of the psychiatric experiences of the first World War, which might well be immediately instituted in connection with our present mobilization tasks. 1.3 per cent of the cases were referred by the psychologists, a rather inexplicable phenomenon in view of the fact that the psychologists had a fine opportunity for observing the soldier in connection with the administration of the intelligence tests; 0.3 per cent were disciplinary cases, and in 3.1 per cent of

the cases the source of detection of the abnormalities was not ascertained.

The second important factor which undoubtedly contributed to the marked lessening of the incidence of neuropsychiatric casualties among the A. E. F. was the manner in which these casualties were managed and treated when they occurred. Before discussing this point, let me again stress the significant prophylactic work which the original elimination technique accomplished. This fact was recognized by a number of American as well as European authorities. After some little experience the average psychiatrist could rapidly survey between 100 and 150 recruits a day with reasonable accuracy. Close and trained observation and a brief but pointed conversation in connection with the physical examination enabled us to detect those who required a more detailed examination. Curiously, but perhaps not so strangely after all, the main difficulties with regard to action on the psychiatrist's recommendation were encountered at the hands of the general medical officers of the disability boards, whereas the line officers who rated their men in terms of conduct, behavior and efficiency, were extremely sympathetic and coöperative.

I dwell upon this prophylactic side of the problem because it is also the most urgent and the most important problem confronting us today in connection with our mobilization. It should be remembered that those accepted into the army in connection with the Selective Service Law are not only obliged to live under military conditions for one year but remain in the army reserve for 10 years thereafter. Apart from the personal suffering of those who might have escaped a breakdown under civil life, had their predisposition to breakdown been recognized, failure to do so creates an incredible economic burden. Of the 68,727 post-war cases under hospital care by the Veterans Administration in June 1940—twenty-two years after the termination of the first World War—20 per cent were neuropsychiatric patients.

Up to the present over one billion dollars have been expended for the care of and for the various benefits granted to these neuropsychiatric patients.

The administrative procedures which are being followed in connection with the present Selective Service Law, will undoubtedly assist the draft boards in detecting a certain number of draftees who are unfit for army life. But we must not deceive ourselves concerning the limitations and shortcomings of such a necessarily rapid and superficial survey. To

be sure, these boards will have before them a great many personal data which the draftee is obliged to supply, a careful scrutiny of which might furnish a hint which should put the examiner on guard. But I think it might help matters if the authorities charged with this important aspect of the work would carefully scrutinize the literature for technical hints in clinical situations similar to those which confront the draft boards. We all recognize the importance of time and coöperation in arriving at a psychiatric diagnosis apart from clinical technique. Permit me to refer to two situations in my own experience which in some ways are not very much unlike the situation confronting the draft boards.

Many years ago, I was engaged in the neuropsychiatric examination of immigrants at Ellis Island. In a paper published following that experience, I pointed out, among other things, that usually we had less than one minute for the preliminary scrutiny of an immigrant, as these people passed before us in single file. It was remarkable how often minor, and what appeared to be insignificant characteristics in posture, gait, general attitude and response to a question or two were sufficient to lead us to select an immigrant for a further examination, which proved to be justified in a remarkably large number of instances.

An effort was made by several of my fellow officers who shared with me the experiences at Ellis Island to examine critically what it was in the nature of hunches or techniques which assisted us in carrying out this difficult job of rapid-fire detection of neurological and psychiatric difficulties. It is estimated that the Medical Advisory Boards of the Selective Service Administration will have about 15 minutes for the secondary, and I think final examination of those suspected of having psychiatric disabilities. It would be well for them to scrutinize whatever literature there is with reference to our experiences in the examination of immigrants in those days when they were coming in at the rate of 100,000 a month at Ellis Island alone.

The other point I wish to touch upon is the importance of coöperation in arriving at a psychiatric diagnosis. Some twenty odd years ago I was engaged in the psychiatric examination of the prisoners at Sing Sing. One of the first difficulties we encountered there was the very prevalent attitude of suspiciousness on the part of the prisoners in connection with any attempt to inquire into what they called their strictly private affairs.

Besides, the benighted lot of prison guards of that day very quickly

dubbed me the "nut doctor" and very quickly succeeded in carrying over to the prisoners the idea that an interview with me meant all sorts of possibilities of further burdening their lot, and came to use it as a threat of punishment. I suppose the situation is very much different with respect to these matters today. But in those early days, when the psychiatric study of prisoners was still a novelty, we had to cope with many serious difficulties in gaining the necessary coöperation of the prisoners. We naturally tested all sorts of devices for overcoming these difficulties and one of these devices seemed to be of great assistance in giving us a hint, at any rate, as to what sort of personality we might be dealing with in a given case. As soon as the prisoner was admitted and practically while he was undergoing his preliminary ablutions, an intelligent, long term fellow prisoner, who assisted us in this work, gave the new inmate a sheet of paper and envelope and suggested that he write a letter to the doctor and address it to him in the sealed envelope. He also hinted that it was part of the prison routine, a little actual deviation from fact which the prison administration agreed to wink at. The letters we received were as a rule very revelatory, indeed, and constituted a very helpful point of departure in connection with the first interview. Especially revealing were those occasional epistles which consisted of just a blank sheet of paper and nothing else.

I am wondering whether, if time permitted, the carrying out of such additional steps in the work of the already overtaxed draft boards would not be a valuable aid in hinting at certain psychiatric difficulties which are somewhat obscure and difficult of detection. I am wondering whether it wouldn't be helpful to ask the draftee to accompany the formal questionnaire which he is asked to fill out by a private and sealed letter to the doctor on the draft board. Some things might come to light in this way which never would be revealed in the official and formal questionnaire. I am aware that in suggesting this rather unofficial and certainly unmilitary deviation from the legal provisions of the Selective Service Law, I am not only exposing myself to the admonition that such informal and perhaps mitigating gesture might well be all right for civil life but has no place in military matters, but I'm also certain to run up against the ancient bugaboo of malingering. As far back as 1916 I published a somewhat detailed study of malingering and came to the following conclusions at that time.

1. The detection of malingering in a given case by no means excludes

the presence of actual mental disease. The two phenomena are not only not mutually exclusive, but are frequently concomitant manifestations in the same individual.

2. Malingering is a form of mental reaction manifested for the purpose of evading a particularly stressful situation in life, and is resorted to chiefly, if not exclusively, by the mentally abnormal, such as psychopaths, hysterics and the frankly insane.

3. Malingering and allied traits, viz: lying and deceit are not always consciously motivated modes of behavior, but are not infrequently determined by motives operative in the subconscious mental life, and accordingly affect to a marked extent the individual's responsibility for such behavior.

4. The differentiation of the malingered symptoms from the genuine ones is, as a rule, extremely difficult, and great caution is to be exercised in pronouncing a given individual a malingerer.

Such experience as I have had in the twenty-five years since then has confirmed me in the views expressed above. Apart from the fact that most authorities agree that the question of malingering played a very insignificant role in the psychiatric experiences of the last war, the resort to malingering on the part of the draftee, especially the malingering of a psychiatric difficulty, should in itself constitute a very strong presumption in favor of considering such an individual unfit for military service. As is so ably pointed out by Mr. Dykstra, the Director of the Selective Service Administration, in his preface to medical circular No. I: "Military life requires that the soldier shall be able to comfortably live in continued close contact with a variegated group of other men. He cannot depend on any self-evolved protective mechanism that sets him apart from his fellows. Military and naval experience is in favor of excluding from the armed forces all persons discovered to have mental or personality handicap of any material degree." Resort to malingering in an attempt to escape military service, should, in my opinion, constitute a sufficient cause for further careful psychiatric observation, if not for rejection forthwith.

It may be that I have devoted a disproportionate amount of the time allotted to me this evening to a stressing of the importance of detecting the mentally unfit draftee. But failure in this phase of psychiatric service is bound to create serious difficulties for the individual soldier as well as for the army. I am convinced, after re-reading the psychiatric

literature of the last war, that the most important contribution which psychiatry made was the prophylactic job of eliminating at the very beginning those who were unfit for military service. Many years ago, Kraepelin's Clinic at Munich issued the dictum that the mere fact of an individual's capacity to develop a psychogenic personality disorder was proof that he was burdened with what they termed a degenerative constitution. I questioned at that time the complete validity of that assertion and still question it today, though not so convincingly as in my youth. But I still doubt whether a predisposition to a failure to manage adequately the devastating experiences of modern warfare necessarily indicates a serious personality defect. The conflict between the forces which condition the desire to live and the avoidance of annihilation, on the one hand, and of those forces within the individual which are responsible for those highly complex attitudes of loyalty, patriotism and honorable behavior as a member of a group, on the other hand, may be unmanageable in the best of men. As a matter of fact, quite a few of the combatants, both officers and men, who subsequently suffered from manifestations of so-called "shell shock" had been decorated for an extraordinary display of bravery and capacity for sustained and unflinching effort under extremely harrowing situations. So that at best we cannot foresee a certain number of these casualties.

Earlier in this paper I stated that I attributed the substantially lower ratio of neuropsychiatric casualties in the A. E. F. as compared with the ratio of the B. E. F. not only to the much briefer participation of our forces in actual warfare but also to the prophylactic measures carried out in this country and to the manner of treating and managing the casualties in the A. E. F. as they occurred at the front.

Here again the country owes a great debt to the late Thomas A. Salmon. I shall briefly quote from the official history the general principles upon which the management and therapy of the neuropsychiatric casualties in the A. E. F. were based. These principles were evolved in consequence of the recommendations made by Salmon's Committee already referred to above. Stated broadly they were: "First, that it is not only in accordance with the best scientific practice to treat soldiers suffering with war neuroses as early and effectively as possible but to do so is an important contribution towards the conservation of man power and military morale; second, that a point of view regarding these disorders based upon a rational conception of their physiological and psy-

chological origin should at all times be maintained and should form the basis for medico-military effort; third, that in neuropsychiatric work, as far as the exigencies of actual service permit, responsibility and leadership should rest in the hands of those who had had special training in this department of medicine. The success attained was due, first, to a clear conception on the part of the highest military authorities of the objectives to be reached and of the general plan to be followed in attaining them, and second, to the cooperation of several hundred specialists in neuropsychiatric work in connection with combat troops, general and special hospitals, courts-martial, camps, classification boards, and prisons."

I shall leave the detailed discussion of therapy to a later section of this review. But in order to indicate by contrast how important the principles quoted above really were in keeping the casualties in the A. E. F. at a uniquely low level, I just want to mention that one way in which commentators classify the therapeutic approaches during the first World War, is to divide them into the authoritarian and the benevolent methods. During the early phases of the war, and indeed almost up to the time when the method employed in the A. E. F. became known, many psychiatric authorities, especially in the German armies, looked upon the war neuroses as akin to malingering; treatment was a matter of punishment and included such measures as isolation (solitary confinement), severe restriction of diet, transfer to excited psychotic wards, application of painful electrical currents, prolonged baths until recovery. A man named Kaufmann was the chief exponent of the most rigorous form of electrotherapy. His method consisted of three phases: (1) suggestive preparation; the patient was told that painful electrical currents would be applied which were certain to cure his condition; (2) application of strong faradic currents for one or two hours; (3) active military exercises. The cure was usually completed in one sitting. This method, originally received with great enthusiasm because of the rapid recoveries, was later generally discarded when fatal cases occurred, and permanency of results was doubted. The above is a good example of what was meant by the authoritarian approach.

The post-war generation of psychiatrists had the unique privilege and the very stimulating experience of living through a period in the history of psychiatry more exciting, more challenging and more pregnant with opportunity for service than at any time before. No one can

question the fact that the psychiatric experiences of the first World War had a great deal to do with this. But I fairly shrink from the task of compressing within the scope of a brief paper a detailed analysis of the factors which made for this cause and effect relationship.

For one thing, never before in the history of medicine had psychiatrists been called upon to deal with such incredibly large numbers of acute psychiatric casualties within such a relatively brief period of time. For another thing, owing to the almost universal presence among these casualties of at least one common etiological factor, namely, the war experience, our then-current and relatively new orientations concerning functional disorders had the first opportunity of being tested on a very large scale. While it is true that both in connection with the immediate call for doing something about these casualties as quickly as possible after their occurrence, as well as in connection with the final assessment of the total experience in the various medical histories of the first World War, various degrees of deviations, dissent and compromise with the then-valid psychoanalytic theories are clearly reflected, nevertheless, nothing emerged from this mass experience of humanity in the throes of anxiety and fear, to challenge successfully the fundamental tenets of Freudian psychology.

As a matter of fact, as soon as the medical officers, and the line officers too, realized the great therapeutic value of turning to the invalid himself for an explanation of his troubles, instead of labelling him on the basis of some preconceived general notions, the shift took place from an authoritarian to a benevolent management of war neuroses. It then also became impossible to fail to recognize, as the younger Miller puts it, that the central motive around which all the clinical manifestations seemed to collect, was the conflict between conscience on the one hand, and instinct on the other. You might substitute, if you wish, for the word conscience the word super-ego, and you might join those who are still engaged today in the fruitless enterprise of classifying and naming the instincts of man. But the essence of the matter is right here. It did not escape the notice of many army psychiatrists in both the A. E. F. and B. E. F. that the shell-shocked patient rarely suffered from an actual bodily injury; that on the contrary, the sustaining of an actual injury, which promised the reward of removal from the scene of war, actually eliminated the necessity for a neurosis. Leri's statement that hysteria never occurred in an open battle, was largely justified. They

recognized the great danger to recovery of a fixation of the initial symptoms, and implemented this by placing psychiatrists as near as possible to the front line.

Naturally, they recognized the importance of fatigue, exhaustion, the shock of nearby explosions and detonations, and the possibility of actual brain concussion; all of the factors contributing to a lessening of ego-resistance which weakened repression, disturbed the balance between the contending forces of the intrapsychic conflict and permitted the emergence of the neurotic symptoms.

The passing in review of such large numbers of war neuroses brought into sharp relief the difficulty of differentiating between the different types of disorders, since, as we know also from civilian experience, strict differentiation is much more possible when the disorder is in an advanced state. Nevertheless, it was considered to be of some therapeutic value to differentiate between the cases as sharply as was possible, and to attempt to discover outside of the great prevalence of common reactions those features which were especially characteristic of the individual invalid under treatment. At Base Hospital 117, which came to be the ideal prototype for base hospital psychiatric organization, research and therapy, the following classification was employed: Neurasthenia, psychasthenia, hypochondriasis, hysteria, anxiety neurosis, anticipation neurosis, effort syndrome, exhaustion, timorousness or state of anxiety, concussion, malingering.

It is hardly worth while to enter into a detailed consideration of the clinical manifestations which led to the above classification. The symptomatology was markedly affected by the time and place of its occurrence and by the immediate precipitating events.

Of more immediate interest is what the literature reflects regarding prognosis, in view of what world events might hold in store for us. Fundamentally, as far as prognosis is concerned, the war neuroses are subject to the same conditions which are operative in civil life. The literature reflects the opinion that prognosis is affected by the age and intelligence of the patient. Naturally, actual breakdowns or pronounced character difficulties before enlistment, and a preponderance of endogenous over exogenous factors, were of bad prognostic significance. This again focuses our attention upon the importance of weeding out the unfit before exposing them to the experiences of war. Furthermore, early treatment and the place where treatment was instituted definitely

affected the outcome, while premature discharge from treatment often led to a recurrence of symptoms. The anticipation of being discharged from treatment sometimes led to a reanimation of the disorder. If this reaction, indicative of a resistance to giving up the secondary gains of the illness, was ignored and the soldier was returned to his unit in spite of the new flare-up of symptoms, the symptoms usually became aggravated during the transport; when he finally rejoined his regiment, he was often in such a state that immediate readmission to a hospital was unavoidable. Thereafter, he occupied hospital beds for weeks or months, and relapsed after discharge. Now these types of reactions are familiar to us in civil practice and I need not dwell upon them in detail. But it is important to recognize that psychiatry could only compromise with the optimum requirements for adequate therapy in the service of military requirements up to a certain point. When these limits were exceeded failure was commonly the result.

War psychiatry, as you see, is an eminently and urgently practical affair. The requirement which was constantly urged upon the psychiatrists to restore the invalided to active duty as soon as possible and in as large numbers as possible frequently came in conflict with the therapeutic principles in the individual case. But it can be said that on the whole, as time went on, psychiatry was increasingly accorded its due recognition and gained for itself in increasing measure favorable working opportunities. Sixty-five per cent of those treated at the advanced clearing stations were returned to front line duty after a few days' treatment.

If what the future holds for us in this country includes the tragic necessity of another expeditionary force, psychiatry is bound to be infinitely better equipped than it was during our last tragic experience to deal with its problems. Of course, the conditions of warfare in 1941 and in the days ahead are very different than they were in the first World War, and unquestionably will bring with them new and untested problems.

For one thing, it is as yet impossible to assess accurately the effect of modern warfare upon the civil and non-combatant population. We are told that a certain widespread "numbness" to daily happenings is affecting large numbers of the English people. It may well be that we shall be obliged to apply to the civil population some of the lessons we learned in connection with the war effort. The techniques for producing

and maintaining the "war of nerves" have attained a high degree of perfection, and steps will undoubtedly have to be taken to insulate some people against the effects of it. For this reason it is very gratifying to know that the draft boards are exercising a very liberal attitude indeed, in the matter of weeding out the unfit. We are told that in England an increasing number of private employers are instituting morale-maintaining measures among their employees, as a defense against the effects of the "war of nerves." In all these measures, psychiatry will undoubtedly be called upon to play an outstanding role.

In conclusion I would urge upon you to read the January, 1941 issue of the American Journal of Sociology, and to re-read Freud's essay on *War and Death* and White's *Reflections on the War and After.* I recommend this, because it might help us individually to re-assess our personal equipment as men and women for its worth in meeting the tasks which will surely be thrust upon us in the days to come. We are committed as a nation to do everything in our power to resist and eventually eliminate the menace that comes to us from across the seas. One of the inescapable features of this task will be the growing necessity of converting our country into what has been termed a Garrison State, where the requirements of the military machine come before everything else, to say the least. At its worst, such a radical change from peacetime pursuits and peacetime freedoms and privileges will call for a readjustment of loyalties which the average man will surely find difficult of accomplishment.

FRIEDRICH AUGUST KEKULÉ

*Architect of Atoms**

HERMAN GOODMAN

It has been said, with truth, of August Kekulé that he bridged the gap from alchemy to modern chemistry . . . Let us define alchemy.

Alchemy: The medieval chemical pseudoscience whose great objective was the transmutation of base metals into gold; the universal cure-agent for disease; the elixir of perpetual life.

Another definition found in books assumes alchemy to mean an infusion or mingling as juice or liquid, especially as extracted from plants for purpose of medicinal ingredients.

What was the world-wide state of alchemy on its road to chemistry in 1865? What was considered Chemistry? Glance at a text professing to be on the subject of chemistry at that period. You are struck at once with the absence of symbols. The shorthand scrawlings and scratchings by which thinking men transferred their thoughts were lacking, for the alchemy turned to chemistry.

Symbols for chemicals, and for chemical reactions, or, for that matter, symbols for structure, were absent—undiscovered, undefined. It was a long and devious travail. Many names are found again and again in a recital of the birth of modern symbols for chemical structure; Berzelius was one. His pupils included Wöhler who forged the chain between inorganic chemistry and organic chemistry. A name linked with that of Wöhler is von Liebig, father of Agricultural Chemistry. von Liebig had a pupil whose name was Friedrich August Kekulé.

Briefly, in a most elementary manner, we review the situation in chemistry at this period. Chemists could and did make analyses. They were able to determine the ingredients. They knew the types of elements. They could enumerate them. The plan of their union was lacking. The arrangement was missing. The blue print of organization was

* Read January 8, 1941 before the Section of Historical and Cultural Medicine of The New York Academy of Medicine.

not available. Linkage became most vital to advance. No one had told about linkage. No one had given a comprehensive and working plan which could withstand criticism. No one had done this: Kekulé found the answer to the riddle in a dream.

Friedrich August Kekulé was born in Darmstadt, September 7, 1829. He showed early talent in drawing and entered the University of Giessen with the intention of studying architecture. Through Liebig's lectures which he attended at Giessen, Kekulé was first attracted to chemistry. Family opposition to his desire to change from architecture to chemistry exiled him to Darmstadt where he managed to study some chemistry. In 1849 he was permitted to return to Giessen where he studied under Will and then again, Liebig. After a year, Liebig told him that he would probably ruin his health if he tried to become a good chemist. As a matter of fact, Kekulé for many years allowed only three or four hours each day for sleep.

In 1851 came an opportunity to go to Paris where Kekulé attended lectures. One day he saw a poster which announced that Charles Gerhardt, ex-professor of Montpellier, was offering lessons in chemistry. He entered his name for these classes. Gerhardt had seen Kekulé's name in Liebig's "Letters on Chemistry." He sent for the young student and offered him the post of assistant. Kekulé did not accept. He continued for a year to attend the lectures and gave much credit later to the inspirational visits he had with his teacher, Gerhardt. Giessen conferred on him the degree of Doctor of Philosophy, July 15, 1852. Then Kekulé went to Switzerland to work with Von Planta, and later to London as assistant to Stenhouse. Kekulé's first independent publication was printed in English and had to do with valence in organic compounds (1854).

During his stay in London, Kekulé was striving to answer the riddle of linkage. The time was about 1856. A glutton for work, and always in need of sleep, Kekulé sought his way by bus to his modest lodging in Clapham Road, after an evening of discussion with his friend, Hugo Müller, in Islington. Riding atop the bus, he fell asleep. He had a strange dream. Molecules gamboled with impish glee. For the first time Kekulé was enabled to discern the nature of molecular motion; to see clearly the precise method of molecular madness. He saw diminutive atoms frequently pair off and be embraced by larger atoms. He saw still larger atoms hold three or four small atoms, while the entire group kept

whirling about in a giddy dance, the large ones forming a chain. Awakened by the cry of the conductor, "Clapham Road," Kekulé spent the night transferring his reveries to paper. Out of this dream grew a system of constitutional formulas representing the structure of molecules of the open-chain type.

Kekulé was homesick in England. He wanted to teach in a German University. With this end in mind he returned to Germany and became a travelling student. In the winter of 1856 he became a dozent at Heidelberg. Here he did some of his most important work in a small private laboratory, a single room with an adjoining kitchen. He had a few pupils, among them Baeyer. It was in this little kitchen that Kekulé finished his work on fulminate of silver, and Baeyer carried out the researches on cacodyl, which subsequently became famous. After two and one-half years Kekulé received a call in 1858 to Ghent, as ordinary professor.

In this same year came "the two great treatises that have exercised so powerful an influence on chemistry—that on the constitution and metamorphosis of chemical combinations; and that on the chemical nature of carbon. We all know today that the theory of valency is the leading guide through all our science, and no one disputes that its main foundation and its eminent value in organic chemistry are primarily due to Kekulé's idea of the quadrivalency of carbon."

Kekulé put the thought forward with diffidence and only in the interest of integrity and progress. His words were, "It seems proper to communicate these conceptions, because, as it appears to me, they furnish a simple and fairly general expression for the newest discoveries, and because, therefore, the use of them may assist in the discovery of new facts."

In his celebrated Textbook of Organic Chemistry (1859), he insisted upon the facts (a) that carbon is uniformly quadrivalent in organic compounds, and (b) that carbon atoms have the remarkable power, unshared, except in a very limited degree by those of other elements, of linking up together to form chains. This idea, which now seems axiomatic, was then highly original. It was scarcely implied in the older theories and was indeed rather foreign to their point of view. Once grasped, however, it gave the key to the constitution of all organic compounds.

It was not Kekulé, however, who first used the bonds with which

we are now so familiar. The complete analysis of organic radicals down to the arrangement of their component atoms was first attempted by a Scotsman, Archibald Scott Couper, in 1858. Through an unfortunate delay, Couper's contribution was not made public until a month after Kekulé had announced the theory. Because of ill health, Couper was unable to elaborate his thesis. Kekulé had a clear mental concept of the facts which were represented symbolically by Couper.

Kekulé, himself, nevertheless, did not at once begin to write graphic formulas, but rather expressed himself with great conservatism. He closed one essay with these words, "I place no more value on these views than they are worth, and I believe that much labor must still be applied before such speculations can be regarded as anything else than more or less elegant hypotheses; but I believe, too, that at least experimental speculations of this kind must be used in chemistry."

In 1859, Kekulé began to construct graphic formulas, but did not employ Couper's bonds. He drew pictures of atoms of different sizes to represent different degrees of "atomicity" or valency. Kekulé used curious diagrams (Kekulé's sausages) with which we are all familiar. This unwieldly notation was very short-lived, for in 1865, Crum Brown introduced the system, in which each "valency" or unit of combining power is indicated by a line. Thus Kekulé's sausages for oxygen and carbon were represented by Crum Brown by the –O– and –C– which we all know. This is a more elegant and equally intelligible device. By 1865, Kekulé had adopted bonds.

In 1861, appeared the first portion of Kekulé's great textbook which emphasized and illustrated the new views with hundreds of examples. The foundations of modern organic chemistry were therein laid. What is more important, the date marks the time when the great contribution of organic chemistry to the historical development of the science as a whole was fully rendered. The earlier theory had broken down because it had failed to explain the reactions of organic chemistry. Slowly and laboriously through the stages of type theory, there had grown up in organic chemistry the theory of structure which was now destined to become dominant in its turn.

Thus we may assume that Kekulé accounted for the straight chain series of paraffin hydrocarbons. He had linked the carbons with each other. He had developed some building plans. He had not yet formed the three dimensional concept which brings us to organic chemistry.

The architect that his family had hoped Kekulé would become was yet to build.

Let us contemplate discoveries by Kekulé relating to the benzol-ring compounds. His influence and his fundamental ideas disclosed the nature of whole classes of compounds which have been of unusual interest to the people of the world ever since.

Benzene substances had originally received this name on account of a peculiar odor possessed by certain representatives. Later it was found that most compounds so classified exhibited very different properties from those of other organic substances of apparently similar structure. Kekulé found it impossible to devise an ordinary chain formula for its molecule. The constitution of benzene became of fundamental importance. At last it occurred to Kekulé that a consistent explanation was to be found in the assumption that the six carbons of benzene were arranged in a ring united by alternate single and double bonds, and with a hydrogen attached to each carbon. There is a distinct interest in Kekulé's account of how the idea came to his mind:

"I was busy writing on my textbook but could make no progress—my mind was on other things. I turned my chair to the fire and sank into a doze. Again the atoms were before my eyes. Little groups kept modestly in the background. My mind's eye, trained by the observation of similar forms, could now distinguish more complex structures of various kinds. Long chains here and there more firmly joined; all winding and turning with a snake-like motion. Suddenly one of the serpents caught its own tail and the ring thus formed whirled exasperatingly before my eyes. I woke as by lightning, and spent the rest of the night working out the logical consequences of the hypothesis. *If we learn to dream we shall perhaps discover truth.* But let us beware of publishing our dreams until they have been tested by the waking consciousness."

Kekulé thus conceived the idea that in the molecule of benzene the six carbon atoms, instead of forming an open chain, have joined together to form a six-membered ring. The formula is now in any standard chemistry textbook.

Kekulé put forward his well-known benzene theory in 1865. It has been pronounced the crowning achievement, in his hands, of the doctrine of the linking of atoms. It is held to be the most brilliant piece of scientific prediction to be found in the whole range of organic chem-

istry. The conception of closed chains, or cycloids, which Kekulé introduced, has shown itself to be capable of boundless expansion.

Kekulé went to the University of Bonn, in the fall of 1867. He finished his first volume of Chemistry of the Benzol Derivatives in the same year. From 1880 to 1887 occurred the publication of the second and third volumes, first as single numbers, prepared with the help of co-workers.

Kekulé always acknowledged the influence of Liebig, Odling and Williamson. Kekulé always distinguished himself as a brilliant and daring thinker, especially devoted to organic chemistry. This branch of the science is indebted to his inspiration for many of its fundamental assumptions. His students spoke of his teaching as lucid; his thinking was called luminous, as well as accurate and concentrated. His language was apt. His delivery was easy and natural. His personality was genial; his humor, happy. He never tolerated slovenly or sloppy work.

His latter years were not productive. Those close to him believed that it was because his researches did not appear to him to be complete. His sense of "finish" and his fastidiousness restrained him from publishing much which he realized fell short of his ideal. Kekulé's greatest service to chemistry remains the development of the theories of molecular structure.

Kekulé died July 13, 1896. His influence lived beyond him. His concept of the carbon ring structure had been truly born of genius. It exercised an influence on all forms of chemistry. Benzene became more than a plaything of science. Modern foundations of constitutional chemistry lie imbedded in the dreams of Kekulé. Researches which Kekulé carried on in his primitive laboratory called for further study with tools fashioned from the results of those early works. In the words Marsh quoted from Landrelt, president of the German Chemical Society at Berlin, on the announcement of the death of Kekulé: "This news will be received with sorrow not only by our society but by the whole chemical world. . . . The works which Kekulé has left behind him belong, as we all know, to the basis of all chemistry."

The constant study of the aromatic compounds in the laboratories of the world during the intervening years has served to confirm Kekulé's hypothesis, which may be considered one of the most thoroughly tested generalizations of science. If we remember that perhaps half the total number of organic compounds at present known are derivatives of

benzene we shall form a just estimate of the value of Kekulé's work.

Let us remember that the side-chain theory of Paul Ehrlich may be traced to the studies of Kekulé and Perkin. The Wassermann serology studies owe their existence to the work of Ehrlich. Salvarsan and its counterparts are due directly to the advances made by Kekulé on the benzene ring structure. The latest tools of mankind against disease, the chemotherapeutic remedies of the sulfonamid group owe their existence in their turn to the dye chemistry of Ehrlich.

On the other side of the ledger, we mention poison gas; death-dealing explosives; incendiary bombs. The dreams of Kekulé—what if they had never been translated into molecules dancing in the fertile brain of the boy who became an architect of atoms instead of bricks!

RECENT ACCESSIONS TO THE LIBRARY

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Adelman, A. L. *Simplified orthodontia.*
[N. Y.], 1941, 47 numb. l.

American Public Health Association. Committee on the Hygiene of Housing. *Housing for health.*
Lancaster, Science Press, 1941, 221 p.

Bisch, L. E. *Why be shy?*
N. Y., Simon, 1941, 265 p.

Clapesattle, H. B. *The Doctors Mayo.*
Minneapolis, Univ. of Minn. Press, [1941], 822 pp.

Cleveland Clinic. *Allergy in practice.*
Phil., Lippincott, [1941], 354 p.

Ehrich, W. E. *Pathology for students and practitioners of dentistry.*
Phil., Lea, 1941, 509 p.

Gerard, R. W. *Unresting cells.*
N. Y., Harper, [1940], 439 p.

Gorsch, R. V. *Perineopelvic anatomy.*
N. Y., Tilghman, [1941], 298 p.

Haworth, N. A. & Macdonald, E. M. *Theory of occupational therapy.*
Balt., Williams, 1941, 132 p.

Hetherington, H. W. & Eshleman, F. *Nursing in prevention and control of tuberculosis.*
N. Y., Putnam, [1941], 316 p.

Lahey Clinic, Boston. *Surgical practice of the Lahey Clinic.* [Reprints].
Phil., Saunders, 1941, 897 p.

Lewin, P. *The foot and ankle.* 2. ed.
Phil., Lea, [1941], 665 p.

McCollum, C. H. *Pills and proverbs.* [autobiography].
Boston, Meador, 1941, 225 p.

McGillycuddy, (Mrs.) J. E. (Blanchard). *McGillycuddy, agent; a biography of Dr. Valentine T. McGillycuddy.*
Stanford Univeristy, Stanford Univ. Press, [1941], 291 p.

Martínez Duran, C. *Las ciencias médicas en Guatemala; origen y evolución.*
Guatemala, Sánchez, 1941, 439 p.

Moseley, E. L. *Milk sickness caused by white snakeroot.*
Bowling Green, O., Ohio Academy of Science, 1941, 171 p.

Prinz, H. & Rickert, U. G. *Pharmacology and dental therapeutics.* 8. ed.
St. Louis, Mosby, 1941, 507 p.

Puente Duany, N. *El linfosarcoma del estómago.*
Habana, Instituto del Radio, Hospital Mercedes, [1940], 94 p.

Samuels, S. S. *Enfermedades de las arterias periféricas.*
México, Unión Tip. Edit. Hispano-Americana, [1941], 402 p.

Taylor, (Mrs.) L. A. (Paz). *Plants used as curatives by certain southeastern tribes.*
Cambridge, Mass., Botanical Museum of Harvard Univ., 1940, 88 p.

Text-book (A) of pathology, edited by E. T. Bell. 4. ed.
Phil., Lea, 1941, 931 p.

Thorndike, A. *A manual of bandaging, strapping and splinting.*
Phil., Lea, 1941, 144 p.

Verovitz, C. H. *Diseases of the veins and lymphatics of the lower extremity.*
Boston, Christopher, [1941], 392 p.

Waddington, C. H. *Organisers & genes.*
Cambridge [Eng.], Univ. Press, 1940, 160 p.

Waisman, H. A. & Elvehjem, C. A. *The vitamin content of meat.*
Minneapolis, Burgess, 1941, 210 p.

Walshe, F. M. R. *Diseases of the nervous system.* 2. ed.
Balt., Williams, 1941, 325 p.

Zilboorg, G. & Henry, G. W. *A history of medical psychology.*
N. Y., Norton, [1941], 606 p.

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

DECEMBER 4—*The New York Academy of Medicine.* Executive Session—Reading of the Minutes. ¶ Papers of the evening. Sterility—a] Diagnosis of sterility in the female, Isidor C. Rubin, Clinical Professor of Gynecology, College of Physicians and Surgeons, Columbia University; b] Treatment of sterility in the female, William H. Cary, Associate Gynecologist and Obstetrician to the New York Hospital; c] Sterility in the male, Robert S. Hotchkiss, Assistant Professor of Urology, New York University College of Medicine. ¶ Report of election of Academy Officers.

DECEMBER 18—*The Harvey Society (affiliation with The New York Academy of Medicine).* The Third Harvey Lecture, "The Adrenal Cortex and Electrolyte Behavior," Robert F. Loeb, Professor of Medicine, Columbia University, College of Physicians and Surgeons.

SECTION MEETINGS

DECEMBER 2—*Dermatology and Syphilology.* Presentation of cases—a] New York University College of Medicine; b] Bellevue Hospital. ¶ Discussion. ¶ Executive session.

DECEMBER 5—*Surgery.* Reading of the Minutes. ¶ Presentation of cases—Cases illustrating the first paper of the evening, George U. Carneal. ¶ Papers of the evening—a] Ambulatory treatment of pilonidal cysts and sinuses (moving picture illustration), George U. Carneal; b] Clinical and physiological studies of the biliary tract in relation to the end-results of operative treatment, Henry Doubilet. ¶ General discussion. ¶ Executive session.

DECEMBER 9—*Neurology and Psychiatry.* Reading of the Minutes. ¶ Presentation of cases—*From the Neurological Service of Bellevue Hospital,* Foster Kennedy. ¶ Papers of the evening—a] An approach to psychological control studies of urinary sex hormones, George Eaton Daniels; Discussion by Sidney C. Werner (by invitation), David Levy; b] Headache in the localization of brain tumor: a re-evaluation of its clinical significance, Harold G. Wolff, E. Charles Kunkle (by invitation) and Bronson S. Ray. ¶ Executive session.

DECEMBER 11—*Pediatrics—Residents' Meeting.* Reading of the Minutes. ¶ Papers of the evening—a] *New York Hospital,* Osteogenesis imperfecta, Samuel W. Dooley (by invitation); Discussion by Samuel Z. Levine; b] *New York Post-Graduate Medical School and Hospital,* Porencephalic cyst, Vincent Larkin (by invitation); Discussion by John Arthur MacLean (by invitation); c] *Long Island College of Medicine,* An unusual case of dermoid cyst, Joseph Caplan (by invitation); d] *Babies Hospital,* Abdominal pain as an epileptic equivalent in children, David M. Greeley (by invitation; Discussion by Rustin McIntosh; e] *Mount Sinai Hospital,* Congenital skin defect, Herman Anfanger (by invitation); Discussion by Bela Schick; f] *Bellevue Hospital,* Rapid treatment of congenital syphilis, Cornelia Morse (by invitation); Discussion by Charles Hendee Smith; g] *Lincoln Hospital,* An unusual case of lymphosarcoma, Harry V. Lomant (by invitation); Discussion by Harry S. Altman.

DECEMBER 15—*Ophthalmology.* Exhibits 7:00 to 8:00—a] Experimental intracapsular cataract extraction—Hanover's canal; b] Motion pictures in color to illustrate above, Jacob Goldsmith (by invitation). ¶ Executive session—Reading of the Minutes. ¶ Presentation of cases—a] A case of Kaposi's sarcoma, Allan Barnert (by invitation); b] A case of interstitial keratitis and acute dacryoadenitis, C. Gregory Barer (by invitation); c] A

case of keratoconus and atopic dermatitis, Bertram S. Kramer (by invitation); d] A case of surgical construction of a lacrimal passage, Loren Guy. ¶ Papers of the evening—a] The use of the Padgett dermatome in ophthalmic surgery, Byron Smith (by invitation); b] Experiences with acetylcholine, Remarks on the treatment of ocular pain, Edward Hartmann (by invitation).

DECEMBER 16—*Medicine.* Reading of the Minutes. ¶ Papers of the evening—a] Physiological mechanism underlying inhalation therapy, L. Corsan Reid (by invitation); b] The miscellaneous uses of inhalation therapy, Virginia Apgar (by invitation); c] Inhalation therapy; its use for pateints other than those with cardiac or respiratory diseases, Emery A. Rovenstine; d] Inhalation therapy in pneumonia, asthma, and pulmonary emphysema: principles and methods, Alvan L. Barach; e] Coordinating gas therapy, Paluel J. Flagg (by invitation). ¶ Discussion.

DECEMBER 16—*Genito-Urinary Surgery.* Reading of the Minutes. ¶ Papers of the evening—a] Renal counterbalance in relation to conservative renal surgery, Louis M. Orr, Orlando, Florida (by invitation); b] Massive hematuria of renal origin, George C. Prather, Boston (by invitation); c] A subtotal perineal prostatectomy and prostatic calculi (moving pictures), Roy B. Henline. ¶ Discussion—Oswald S. Lowsley, Nathaniel P. Rathbun.

DECEMBER 17—*Otolaryngology.* Reading of the Minutes. ¶ Papers of the evening—a] Osteomyelitis of the skull and the repair of osteomyelitic defects in the calvarium, Albert C. Furstenberg, Ann Arbor, Michigan (by invitation); Discussion by Joseph E. King, Andrew A. Eggston. ¶ General discussion. ¶ Executive session.

DECEMBER 19—*Orthopedic Surgery.* Reading of the Minutes. ¶ Presentation of cases—a] A case of post-laminectomy with herniation of the cauda equina relieved by spine fusion, Maurice H. Herzmark (by invitation). ¶ Papers of the evening—a] The technique for removal of herniated nucleus pulposus without laminectomy, Edwin M. Deery; Discussion by Alan DeForest Smith; b] Tumors of cauda equina—diagnostic consideration with relation to low back pain—operative results, Ira Cohen, Abraham Kaplan (by invitation); Discussion by Leo Mayer. ¶ General discussion, Alan De Forest Smith, Leo Mayer, David M. Bosworth, John R. Cobb and Mather Cleveland. ¶ Executive session.

DECEMBER 23—*Obstetrics and Gynecology—Program presented by The Margaret Hague Maternity Hospital, Jersey City.* Executive session—Reading of the Minutes. ¶ Papers of the evening—a] New method of determination of escape of amniotic liquid, George A. Bourgeois (by invitation); b] Deciduoma of the cervix and endometriosis in pregnancy, Nicholas M. Alter (by invitation); c] Management of premature separation of placenta, S. A. Cosgrove, D. F. Conway (by invitation). ¶ General discussion.

AFFILIATED SOCIETIES

DECEMBER 15—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* Paper of the evening—Tissue changes following irradiation, Shields Warren (by invitation). ¶Discussion—Fred Stewart (by invitation), Arthur Purdy Stout (by invitation). ¶ Executive session.

DECEMBER 18—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* ¶ Presentation of cases—a] A case of Weber-Christian disease, Robert Kritzlar (by invitation); b] A case of temporal arteritis, Edith Sproul (by invitation). ¶ Papers of the evening—a] Histoplasmosis, Henry E. Meleney (by invitation); b] The distribution of intimal atheromas in the arteries of rabbits on high cholesterol diets. Sigmund L. Wilens (by invitation). ¶ Executive session.

THE INTER-AMERICA DIVISION OF THE ACADEMY

The Council of the Academy on December 17, 1941 authorized the establishment of an INTER-AMERICA DIVISION of the Bureau of Clinical Information for the special purpose of assisting visiting physicians from the sister republics of South and Central America and the West Indies.

THE NEW YORK ACADEMY OF MEDICINE extends a welcome to all members of the medical profession from other countries of the Western Hemisphere. Visiting physicians are invited to make the Bureau their headquarters while in the city.

THE LIBRARY is one of the largest of its kind in the United States. Its files of American and foreign periodicals are very complete. A bibliographic and photostat service is available at the usual library rates.

MEETINGS. Besides two Stated Meetings of the Academy held each month, there are monthly meetings of the eleven different groups of members organized into Sections devoted to various branches of medicine. Many other medical societies of the city, including a number of affiliates, meet at the Academy.

LECTURES. A series of Friday afternoon lectures on subjects of special interest to the practitioner is given each year, beginning in November.

THE ANNUAL GRADUATE FORTNIGHT is held in October on a subject of outstanding importance in the practice of medicine and surgery and consists of meetings at the Academy, coordinated clinics in selected hospitals, and a large scientific exhibit.

BUREAU OF CLINICAL INFORMATION. The Committee on Medical Education maintains at the Academy a Bureau of Clinical Information where details may be obtained regarding opportunities for postgraduate medical study in Greater New York and also in other cities of the United States.

The Bureau publishes a *Daily Bulletin* which announces the meetings, lectures, conferences, hospital rounds and other interesting medical activities of the day. A *Surgical Bulletin*, issued the previous evening, announces the major operative work of leading surgeons of the city, performed in the clinics of more than seventy important hospitals and other medical centers in the United States.

A Bulletin of Approved Non-Operative Clinics is also published. This Bulletin lists clinics in thirty-three special subjects held in twenty-nine general and special hospitals. Copies of the Bulletins and of catalogues describing postgraduate medical courses offered in Greater New York may be obtained at the Bureau or will be mailed upon request.

DEATHS OF FELLOWS

BOZSAN, EUGENE JOHN: 1130 Park Avenue, New York City; born in Kisuarda, Hungary, December 17, 1889; died in New York City, December 4, 1941; graduated in medicine from the Royal Hungarian University of Sciences, Budapest in 1913; elected a Fellow of the Academy April 7, 1932.

Dr. Bozsan was attending skeletal surgeon at the Morrisania Hospital and associate in general surgery at the Hospital for Joint Diseases. He was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a diplomate of the American Board of Surgery, a member of the American Association for the Surgery of Trauma, and a member of the State and County Medical Societies.

DUFFY, JAMES JOSEPH: 862 Park Avenue, New York City; born in Webster, Massachusetts, May 17, 1892; died in New York City, December 13, 1941; graduated in medicine from Harvard Medical School in 1919; elected a Fellow of the Academy November 3, 1927.

Dr. Duffy was assistant professor of radiology at Cornell University Medical College, associate attending surgeon and assistant radiologist to Memorial Hospital, attending surgeon to St. Vincent's Hospital, and consulting surgeon to the New York Infirmary for Women and Children, St. John's Hospital at Long Island Ctiy, St. Agnes Hospital at White Plains, and St. Mary's Hospital in Brooklyn. He was a diplomate of the American Board of Radiology, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a member of the American Radium Society, and a member of the State and County Medical Societies.

HONEGGER, OSCAR PETER: Lake Mahopac, New York; born in Pittsburgh, Pennsylvania, March 17, 1855; died in Lake Mahopac, December 25, 1941; graduated in medicine from the University of Heidelberg in 1879; elected a Fellow of the Academy June 2, 1887.

NILES, WALTER LINDSAY: 115 East 61 Street. New York City; born in Lebanon, New York, January 2, 1878; died in New York City, December 22, 1941; graduated in medicine from Cornell University Medical College in 1902; elected a Fellow of the Academy February 6, 1908; and served the Academy as secretary of the Section of Medicine in 1911, and chairman of that Section in 1912; as a member of the Committee on Admission, 1915-1921; as a member of the Committee on Public Health Relations, 1917-1929; as a member of the Committee on Medical Education in 1929; as vice-president of the Academy, 1934-1936; as a member of the Board of Trustees, 1928-1932. Again, in 1936, he became a member of this Board and in 1937 assumed its chairmanship, which office he held until his death.

Dr. Niles was professor of clinical medicine at Cornell University Medical College since 1916 and was the dean from 1919 to 1928. He was consulting physician to Bellevue Hospital, New York Infirmary for Women and Children, Willard Parker, Jamaica, Mather Memorial, Southampton and Nassau Hospitals, and attending physician to the New York Hospital. He was a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association, a member of the administrative board of the New York Hospital, and a member of the Cornell Medical College Association, the American Clinical and Climatological Association, the Association of American Physicians and the State and County Medical Societies.

PATON, STEWART: 208 Stratford Road, Baltimore, Maryland; born in New York City, April 19, 1865; died in St. James, Long Island, New York, January 7, 1942; received the degree of M.A. from Princeton University in 1886 and graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1889; elected a Fellow of the Academy March 2, 1893.

Dr. Paton was a former associate in psy-

chiatry at Johns Hopkins University and director of the Laboratory of the Sheppard and Enoch Pratt Hospital, Baltimore; lecturer on neurobiology at Princeton University and on psychiatry at Columbia University. From 1926 to 1928 he was consultant on mental hygiene and lecturer on psychiatry at Yale University. He was a trustee of the Carnegie Institution at Washington, a trustee of the Josiah Macy Jr. Foundation, a Fellow of the American Association for the Advancement of Science, a member of the Eugenics Research Association and its president in 1919, and a member of the American Philosophical Society, the American Neurological Association, the American Medical Association and the County and State Medical Societies.

Dr. Paton was the author of several books, among them the "Text-Book of Psychiatry for Use of Students and Practitioners of Medicine," "Human Behavior," "Signs of Sanity and the Principles of Mental Hygiene," and "Prohibiting Minds."

THOMAS, WILLIAM STURGIS: 1141 Fifth Avenue, New York City; born in Poughkeepsie, New York, October 11, 1871; died in New York City, December 21, 1941; graduated from the Medical Department of the National University, Washington, D. C. in 1892; elected a Fellow of the Academy December 15, 1904.

Dr. Thomas was associated with the St. Luke's Hospital for about forty years and served from 1921 until his retirement in 1940 as consultant in immunology and director of the allergy clinic. He was a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association, a member of the Society for the Study of Asthma and Allied Conditions, and a member of the State and County Medical Society.

Dr. Thomas was the author of "Textbook on Asthma" and contributed numerous articles to medical journals on allergy, asthma, and allied subjects.